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THE EFFECT OF COBALT AND IRON SALTS ON THE ANAEMIA OF PREMATURITY

BY

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Premature infants tend to exhibit higher blood values at birth than full-term infants, but show a more rapid and prolonged fall in both haemoglobin and red cells and frequently develop anaemia which is maximal at about the third month (Parsons and Hawksley, 1933). Landé (1919), using a Sahli method (standard 17·2 g. equals 100%) found average levels of 60 to 65% haemoglobin and average red cells of 3·3 m./c.mm. at the third month. In many cases the count fell to 50%. She quotes Knuckel who gave an average level of 47% at 3 months though the red cells were proportionately less reduced and averaged 4 million. Abt and Nagel (1932) divided their cases into those of six to seven months' gestation and those of eight months' gestation. The former reached the lowest point at eight to 12 weeks with average levels of 54% haemoglobin and 3·3 million red cells. The haemoglobin level of infants of eight months' gestation fell to 60% at 8 weeks, with 4·0 million red cells (16·9 g. haemoglobin equals 100%, Newcomer). In another series (Merritt and Davidson, 1934) of untreated premature infants the haemoglobin fell from 21·7 g. at birth to 11·0 g. at 2 months of age. The red cells averaged 5·54 million at birth and fell to 3·91 million at 2 months. In a series of immature infants the counts fell from 23·0 g. haemoglobin and 5·81 red cells to 11·8 g. and 4·04 red cells during the same period. In all cases the counts remained more or less stationary to 10 months of age, when the period of observation ceased. Herz (1928) considered values below 13 g. at 2 to 4 months denoted anaemia. Of 103 premature infants investigated, 16 had values of 8 to 12 g. at this age whereas only one full-term infant reached a value as low as 12 g. Mackay (1935), investigating prematures of birth weight 3-4 lb., found a fall from 149·9% at birth to 73·4% at the tenth week. Infants of birth weight approximately 5 lb. showed a similar fall from 146·6% at birth to 76·0% at the fourteenth week. Most observers agree that the anaemia of prematurity is a self-limiting disease with spontaneous recovery after about the fourth month. In the series of Abt and Nagel (1932), infants of seven months' gestation reached values of 68% haemoglobin and 4·9 million red cells at 6 months, and infants of eight months' gestation, 69% haemoglobin and 4·9 million red cells at 6 months. Mackay's cases (1935) had risen to 81·7% (birth weight 3-4 lb.) and 80·8% (birth weight approximately 5 lb.) at 26 weeks of age. These cases were all untreated and form a contrast to those of Merritt and Davidson (1934), who reported no significant changes in the counts from the time of maximum anaemia to the tenth month. If the initial fall has been very marked, recovery is delayed and may be incomplete.

The pathogenesis of the anaemia of prematurity is obscure. Lichtenstein (1921) found a negative iron balance in four premature infants not receiving additional iron, but this work was not confirmed by Snelling (1933). Josephs (1936) divided the anaemia of prematurity into three stages. The early physiological anaemia during the first two months, in which there is no response to haemopoietic agents and the reticulocytes are low, constitutes the first stage. The second stage is marked by a gradual rise in the red cells, the haemoglobin remaining stationary. At this stage hypochromia may develop and the response to iron is usually good. He considered a mild iron deficiency was of importance in the development of this phase. The third phase is identical with the hypochromic anaemia of full-term infants but is more marked. He believed that the iron stores of the premature infant are deficient only in relation to the more rapid rate of growth. This view is also held by Mackay (1935). Josephs also thought that iron deficiency does not occur before the third month except in cases of loss as in haemorrhage or excessive haemolysis, but that after the third month iron deficiency becomes increasingly important. He concluded that in premature infants

there is either a failure to utilize iron or an inability to synthesize haemoglobin sufficiently rapidly. He also emphasized the high infection rate in premature infants with particular reference to syphilis as a cause of premature birth, and of consequent aggravation of existing anaemia. Abt (1935) also reviewed the possible causes of anaemia in premature infants and suggested that the smaller total blood volume at birth results in a poor supply of iron from endogenous sources. Iron supplies are exhausted between the third and sixth months owing to the rapid rate of growth and an iron deficiency is thus produced. He also suggested a functional incapacity of the haemopoietic system. This possibility was confirmed by marrow investigations (Lichtenstein and Nordenson, 1939). The bone marrow of 25 premature infants showed a marrow which was immature though hyperplastic, and maturation did not proceed along normal lines. This picture was correlated with signs of immaturity in the peripheral blood and with an anaemia which was maximal at the third month. The most severe anaemia coincided with the greatest immaturity of the marrow. After the third month the marrow picture improved considerably but some degree of immaturity persisted throughout the first year. These findings compare with the hyperplastic yet insufficient marrow found in other anaemias. Landé (1919) examined the marrow in 10 premature infants without finding any cause for their anaemia though she mentioned the deficiency of granulocytes which is associated with the poor resistance to infection of these infants.

The response to treatment of the anaemia of prematurity is disappointing. Intramuscular blood has been tried with unsatisfactory results (Landé, 1919; Mackay, 1935). Liver, either alone or in combination with a hog's stomach preparation, had no beneficial effect (Abt and Nagel, 1932). Iron and ammonium citrate with or without liver extract has been found to minimize the severity of the anaemia but not to prevent it entirely (Abt and Nagel, 1932; Merritt and Davidson, 1934). Merritt and Davidson state that observers are agreed that anaemia in premature infants cannot be completely prevented and that those reporting success with iron have always used large doses. Various remedies employed without success include exposure to fresh air, dietary methods with substitution of fruit and vegetables for an exclusively milk diet, vitamin B, hog's stomach, and copper alone or with iron. The diversity of treatment investigated indicates that no entirely satisfactory method has yet been found. The best is probably iron in some form with transfusion reserved for the most severe cases. The benefits of this, however, tend to be transitory and repeated transfusions are often necessary. Although spontaneous recovery from the anaemia is usual and pallor is often the only symptom, the development of any anaemia in infants already handicapped by prematurity may be serious. This is chiefly due to the increased risk of infection in anaemic children, and premature infants are already particularly prone to infections. Blood transfusion is a skilled procedure in these small infants and is not entirely free from risk, and an easily administered and well tolerated drug effective in the prophylaxis and treatment of the anaemia of prematurity would be of some clinical importance.

The blood picture in this anaemia is of normocytic normochromic type with a low reticulocyte count, and in these features it shows a marked similarity to the anaemia associated with infection. It has been suggested by Wintrobe, Grinstein, Dubash, Humphreys, Ashenbrucker and Worth (1947) that cobalt may be needed in the synthesis of haemoglobin in the anaemia of sepsis, and Vaughan (1948) referred to this in a paper on the anaemia of sepsis and trauma, and suggested cobalt as a possible treatment of anaemias resulting from infection. It was because of the similarity between the anaemia of sepsis and that of prematurity that we decided to try the effect of cobalt in premature infants.

There is a considerable literature on the experimental use of cobalt in producing polycythaemia both in normal and anaemic animals. Orten, Underhill, Mugrage and Lewis (1932), Orten (1936) and Stanley, Hopps and Hellbaum (1946), studied its effect on rats, Frost, Elvehjem and Hart (1941) on dogs, and Davis, McCullough and Rigdon (1945) on ducks. Cartwright (1947) gave a comprehensive review of the experimental work. In treated animals the haemoglobin and red cell counts both showed considerable increases over values for normal controls. Wintrobe *et al.* (1947) and Gubler, Cartwright and Wintrobe (1950) studied the effect of cobalt on rats made anaemic by the production of turpentine abscesses. They found that animals to which cobalt was given in addition to turpentine not only failed to develop anaemia but actually became polycythaemic. In rats already made anaemic the administration of cobalt rectified the anaemia. Rats treated with turpentine had low plasma iron levels and raised erythrocyte protoporphyrins, results also found in patients with anaemia associated with sepsis. The blood iron level of rats treated with turpentine and of those receiving turpentine and cobalt showed highly significant differences, and it is concluded that cobalt favourably influences the utilization of iron for haemoglobin synthesis. All the rats in Gubler's experiments were receiving iron

at the time, and increased absorption of iron was not demonstrated after cobalt treatment, thus suggesting that cobalt favours increased utilization of available iron. This view is supported by the work of Kato and Iob (1940) on the influence of cobalt on iron storage. These authors found that animals receiving large doses of iron over long periods stored iron in the spleen and to a lesser extent in the bone marrow. When cobalt was given together with iron, no iron was found in these organs, but the total iron content of the blood was raised 24-58% above control values. This bears out the suggestion that cobalt enables iron to be more completely utilized for haemopoiesis than when iron is given alone. In animals there is a slight reticulocytosis maximal about the fourth day with a secondary rise reaching a peak on the twentieth to twenty-fourth day (Orten, 1936). These responses were observed both in young and in adult animals. In ducks the bone marrow shows a hyperplasia of the erythroid elements up to the fourteenth day, but by the nineteenth day there is evidence of hypoplasia of the erythroid series (Davis *et al.*, 1945). It is possible that the initial rise in peripheral blood levels is due to erythropoietic stimulation of the marrow but that the maintenance of polycythaemia may in part be due to a depressed rate of blood destruction. Kato and Iob also studied the marrow during cobalt treatment and found that at the height of polycythaemia there was a distinct hyperplasia of all marrow elements but especially of the erythroid series. They did not note any evidence of toxicity to the marrow.

Experience of the effect of cobalt on weight and appetite seems to vary. Wintrobe *et al.* (1947) found that cobalt impaired weight gain more than turpentine injections in a series of rats, though both failed to gain as well as control animals. They thought that failure might be associated with anorexia. Orten *et al.* (1932) also found that rats on cobalt gained less than the controls. In ducks, however, there was no difference between treated cases and controls (Davis *et al.* 1945). Orten and Bucciero (1948) found that treated animals ate more per 100 g. body weight than control animals. Milk contains extremely small amounts of cobalt (Frost *et al.*, 1941); therefore if a true cobalt deficiency exists in man, young infants would be liable to such a deficiency. Frost and his co-workers found that about half the dogs investigated, which were fed on an exclusive milk-iron-copper diet, showed evidence of cobalt deficiency in that the blood responded to doses as small as 0·1 mg. daily. It is an established fact that sheep and cattle fed on pastures where the soil is deficient in cobalt develop a wasting disease in which anaemia is a prominent feature (Gall, Smith, Becker, Stark and Loosli, 1949), but so far there are no conclusive reports of cobalt deficiency in man.

Therapeutic reports of cobalt in the treatment of anaemia in man are few and there is no reference to its use in premature infants. Waltner (1930) first discussed its uses in the anaemia of childhood although it had already been tried by Antal in 1894 as an antidote to cyanide poisoning, and a cobalt-arsenical preparation had been used as a general tonic. Waltner treated 21 children with secondary anaemia, with 14 favourable results. After four to five weeks the red cells had risen by 32·5% from an average starting point of 3·36 million/c.mm. He found that cobalt had little effect on the haemoglobin and advised that it should be given in combination with iron. He also treated 57 children with cobalt used as a tonic, and noted beneficial effects on the appetite and weight in 31, who averaged a weekly gain of 250 g.; 26 failed to respond. Baxter (1939) gave 2-30 mg. of cobaltous chloride daily to eight patients with hypochromic anaemia. He obtained an average daily rise of 18,800 red cells and 0·11% haemoglobin, but considered cobalt inferior to iron and of no use in hypochromic anaemia. Three cases developed anorexia, two nausea, one vomiting, one pruritis and one urticaria, a high incidence of toxic manifestations. Cronin (1939) treated one case of lymphatic leukaemia and one case of hypochromic anaemia with 30 mg. daily. There was no haematological response in either case. Kato (1937) reported a series of infants with haemoglobin levels below 11 g. They received iron and ammonium citrate, 0·5 g. daily, and 25-50 mg. cobalt sulphate was given to 37 infants who failed to respond to iron. Eighteen received cobalt and iron from the start. Seventy-six per cent. of those treated showed satisfactory responses, the haemoglobin, red cells and haematocrit increased in parallel, and the majority of cases made the best progress within two weeks of starting treatment. The average weekly rise in red cells was 250,000, in haemoglobin 0·6-0·9 g. %, and in haematocrit readings 1-1·5%. There were no toxic effects. Caussade, Franck and Petitdant-Monniot (1947) used cobaltous chloride, 10 mg. daily, on five infants, and 20 mg. daily on eight children aged from 2 to 7 years. They obtained satisfactory results in all but two infants in whom treatment was interrupted because of infection. The general condition improved and the infants had increased vigour following treatment.

The effect of cobalt on the anaemia of infection has been studied by Robinson, James and Kark (1949) who treated nine patients with chronic osteomyelitis or soft tissue suppuration. They used

cobaltous chloride in doses of 20-60 mg. daily for two to 11 weeks. Reticulocyte responses occurred as early as the fourth day and were maintained throughout treatment. In all cases a return to normal blood values was obtained. Two patients had slight anorexia. Cobalt has also produced haematological responses in subjects without anaemia (Berk, Burchenal and Castle, 1949). Eight patients received 100 mg. cobaltous chloride daily and reticulocyte responses occurred in six cases. Dosage was then increased to 200 mg. daily and the two remaining patients developed a reticulocytosis. The others reached a higher peak than they had attained on the smaller dose. All cases showed moderate increases in haemoglobin, red cells, and haematocrit readings. Two patients received 300 mg. daily with higher responses than the first eight, and one case required venesection after treatment. Increasing doses, up to 400 mg. thrice daily, produced anorexia in one case after six weeks, and severe nausea and vomiting after two weeks in the second case. Six cases of pernicious anaemia in remission developed symptoms and treatment had to be stopped. Of 32 anaemic patients reported in the same paper, five with chronic sepsis showed a good response. One of two patients with carcinoma of the stomach, and a case of Cooley's anaemia, also responded. Three of 10 patients with lymphoma gave a doubtful response; there was no effect on anaemia associated with cirrhosis of the liver or chronic renal disease. Apart from mild alimentary symptoms, two patients developed precordial pain with evidence of myocardial infarction. All symptoms were relieved after cobalt was stopped. Because of its similarity to the anaemia of sepsis in which cobalt had proved of some value, Shen and Homburger (1951) treated 16 patients with anaemia associated with advanced cancer with cobaltous chloride, 60-240 mg. daily. Nine patients had a reticulocyte response and three showed elevation of the blood count to normal levels. Two failed to respond at all, two died before any rise could be expected although they had a reticulocytosis, and two were unable to tolerate the drug. The authors noted a high incidence of toxic reactions including nausea, vomiting, anorexia, muscle pains and angina. Even in patients with a satisfactory haematological response, the clinical condition remained unsatisfactory and patients continued to complain of depression and apathy in spite of normal blood levels. The only series where bone marrow studies have been used to confirm the peripheral blood findings is that of Virdis (1952) who treated nine children aged 1 to 3 years with alimentary anaemia or anaemia associated with infection. One case of macrocytic anaemia failed to respond but the others all showed increases in red cells, though the haemoglobin remained relatively low. He recommended the simultaneous administration of iron to secure corresponding rises in haemoglobin. In all but three cases marrow puncture showed stimulation of erythropoiesis and a fall in the myeloid-erythroid ratio. Cobaltous chloride was used in daily doses of 15-20 mg. by mouth or 1 mg. intramuscularly.

Present Investigation

Premature infants born at four maternity units took part in this investigation, which covered a period of 18 months. Cases from three units were used for the whole time and those from the fourth for the first year only. In all, 126 consecutive infants were investigated and 83 were followed up for six months or longer. Four further infants were excluded from the series, one on account of severe haemorrhage from the cord and three because of death in the neonatal period. Red cell counts were made with an improved Neubauer counting chamber using normal saline and methyl violet as a diluting agent, and the haemoglobin was estimated by the Sahli method using a standard of 14 g. haemoglobin equals 100%. In the neonatal period the blood-acid mixture was allowed to stand an hour before readings were made, as Whitby and Britton (1950) point out that foetal haemoglobin takes longer to convert to acid haematin than the adult type, and falsely low results may be obtained if this is not taken into account. The same counting chamber, standard and glassware were used throughout the investigation to obtain comparable results, and all blood was taken and examined by one observer (B.L.C.). Blood was obtained in all cases by heel puncture.

The cases were divided at random into four groups as follows: Group I acted as controls. Group II received cobalt sulphate, 10 mg. daily by mouth, from the first to the twelfth days of life inclusive. Group III received cobalt sulphate, 20 mg. daily by mouth, from four to eight weeks. Group IV received 20 mg. as above together with gr. $4\frac{1}{2}$ of ferrous sulphate daily from four to eight weeks.

The cobalt sulphate used was the B.D.H. analar salt which is freely soluble in water and practically tasteless. The iron mixture was prepared according to Mackay's formula, and was given in three divided doses.

Blood counts were made in all cases at birth, 1 week, 2 weeks, 1 month, and at monthly intervals to 6 months. After 6 months the blood was examined at 9 months, and again at 1 year in those cases still attending. In the early stages of the investigation we were anxious to ascertain if the administration

of cobalt from one to 12 days influenced the physiological fall during the first weeks of life and counts were therefore made on the fourth, eighth and twelfth days of life in 20 cases receiving cobalt and 18 controls. This was discontinued owing to the negative results. We also wished to ensure that a month's continued cobalt from four to eight weeks did not produce polycythaemia. Eighteen cases on therapy from four to eight weeks, 14 controls and 12 Group II cases had counts at 6 weeks of age. These counts lay midway between those at 1 month and 2 months in the majority of cases and the results are therefore not included in our table.

We adopted an arbitrary level at which further treatment was instituted if anaemia developed during the course of the investigation. Cobalt sulphate, 20 mg. daily, was given to any infant whose red cell count fell below 2·5 m./c.mm. if the haemoglobin was below 70% at that time, and ferrous sulphate, gr. 4½, was given to infants with haemoglobin below 70%, and infants of 6 months with haemoglobin below 75% for two consecutive months were also given iron in order to prevent a severe iron deficiency anaemia. In cases requiring additional iron therapy at 6 months the blood was examined monthly until therapy ceased and satisfactory blood levels were obtained.

All infants were either breast fed or received dried or evaporated milk made up 20 calories to the ounce. Vitamins A, D and C were started as soon as feeding was satisfactorily established, usually at about the tenth day, and solids were introduced in all cases between 3½ and 5 months. Where possible the infants attended special follow-up clinics attached to the maternity unit, but where distance or domestic duties made this impossible they were visited at home. Records of weight and clinical progress were made at each visit.

Results

During the first 12 days of life 20 cases receiving cobalt and 18 controls had blood counts on the fourth, eighth and twelfth day. The average fall of haemoglobin and red cells below birth level on each day of bleeding are shown in Table 1. The infants receiving cobalt showed a less pronounced fall in both haemoglobin and red cells, but the differences are not marked. The effect of the early administration of cobalt on the later counts, i.e., from one month onwards, will be discussed later, but it appears that cobalt has little effect in modifying the fall during the first two weeks.

The results of counts from birth to 1 year have been expressed in two ways. All cases have been grouped according to the treatment they received and in addition divided into those of birth weight 4½-5½ lb. and those of birth weight under 4½ lb. These results are shown in Tables 2 and 3. Tables 4 and 5 show the same cases rearranged according to the gestation period. Cases of eight to nine months' gestation are shown in Table 4, and cases of six to eight months' gestation in Table 5. It was felt that this would give a more accurate picture of the results as the smallest infants in our series were not always the most premature by dates or in behaviour. Once an infant required additional therapy its data were removed from these tables and findings in such cases are expressed separately. For statistical purposes all cases were analysed together irrespective of birth weight to enable larger numbers to be used for comparison, and the statistical analysis only extends over the first six months of life. These analyses are shown in Tables 6 and 7. The study of the last six tables shows surprisingly little difference in the values for controls between the two birth weight groups. When the cases are arranged according to gestation period, however, there is a marked tendency for those of six to eight months' gestation to develop low haemoglobin values after the age of 4 months, compared with the infants of 8 to 9 months' although the red cell counts remain comparable in both groups. In the treated cases the figures for both birth weight groups and both gestation groups are extremely close and initial weight appears to play little part in the response to treatment. The statistical analysis shows that infants receiving cobalt from one to 12 days (Group II) had slightly higher average haemoglobin and red cell counts than the controls (Group I). The difference

TABLE 1

AVERAGE FALL OF HAEMOGLOBIN AND RED BLOOD CELLS BELOW BIRTH LEVELS DURING FIRST 12 DAYS

Group	4th Day		8th Day		12th Day		No. of Cases
	Hb. (%)	R.B.C. (m.)	Hb. (%)	R.B.C. (m.)	Hb. (%)	R.B.C. (m.)	
I	6·55	0·40	16·77	0·82	23·71	1·26	18
II	5·85	0·42	10·95	0·80	22·00	0·88	20

Group I. Controls. Group II. Cob. Sulph., 10 mg., 1-12 days.

in haemoglobin content at 2 months and four of the six differences in average red cell counts, those at 1, 2, 4 and 5 months attained statistical significance. Up to the age of 6 months control values for both haemoglobin and red cells are well below those for either Group III or Group IV cases, whether cases are arranged by birth weight or by gestation period. In view of the small effect of the early administration of cobalt the data for this group of infants have been amalgamated with those for the control group to give a more dependable standard against which to assess any effect of giving cobalt from one to two months. Infants who received cobalt from 1 to 2 months (Groups III and IV combined) had a significantly higher average haemoglobin content and red cell count at each examination from 2 months onwards than Groups I and II combined. Infants in Group IV had statistically significant higher haemoglobin contents from 4 to 6 months than Group III cases who also received cobalt but no iron. At this stage iron deficiency becomes important in the development of anaemia in premature infants, and these results were to be expected. The red cells appear unaffected by iron. Counts at 9 months and 1 year have been included in our tables as a matter of interest, but the numbers are too small to be of any value for statistical purposes. Those control cases which had reached nine months without developing anaemia appeared by this time to have satisfactory blood levels and to have reached the values of the treated cases.

The counts in three cases fell to the values set as

TABLE 2

AVERAGE HAEMOGLOBIN CONTENT AND RED CELL COUNTS FROM BIRTH TO 1 YEAR IN INFANTS OF BIRTH WEIGHT OVER 4½ lb.

Age and Group		Average Counts		Maximum Counts		Minimum Counts		No. of Cases
		Hb. (%)	R.B.C. (m.)	Hb. (%)	R.B.C. (m.)	Hb. (%)	R.B.C. (m.)	
Birth	I ..	21·8	5·79	24·9	7·20	15·7	4·58	31
	II ..	21·7	6·03	25·2	6·74	15·7	5·26	16
	III ..	20·7	5·90	25·2	7·20	14·3	4·86	14
	IV ..	21·4	6·07	25·2	7·12	16·8	5·50	12
1 month	I ..	13·4	4·00	17·6	5·50	10·6	2·92	18
	II ..	14·1	4·53	18·9	5·74	10·9	2·59	14
	III ..	13·3	4·04	16·0	5·76	8·8	2·62	14
	IV ..	15·2	4·12	18·7	4·88	12·5	3·16	12
2 months	I ..	10·8	3·55	12·6	4·36	9·4	2·64	15
	II ..	11·9	3·82	16·1	4·82	9·2	3·28	13
	III ..	12·5	4·13	17·5	5·32	9·8	3·52	14
	IV ..	12·9	4·30	16·0	5·90	10·8	3·32	12
3 months	I ..	10·8	3·75	12·6	4·48	9·8	2·84	13
	II ..	10·8	3·71	14·8	4·34	9·7	3·20	11
	III ..	11·8	4·50	14·0	5·56	9·0	3·60	14
	IV ..	12·3	4·41	14·1	5·70	11·2	3·72	10
4 months	I ..	10·8	3·70	12·6	4·70	8·4	2·59	13
	II ..	11·8	4·30	15·4	5·02	9·2	3·44	11
	III ..	11·6	3·36	13·0	5·48	7·4	3·65	14
	IV ..	12·7	4·31	14·6	5·24	12·0	3·66	11
5 months	I ..	11·3	4·04	13·2	4·98	9·8	3·08	11
	II ..	12·0	4·46	15·0	4·92	9·7	3·92	11
	III ..	11·8	4·50	13·9	5·50	9·9	3·95	12
	IV ..	12·0	4·21	13·7	4·74	11·5	3·58	9
6 months	I ..	11·2	4·15	12·7	5·26	8·0	3·48	11
	II ..	11·6	4·35	14·0	4·79	9·2	3·66	9
	III ..	11·9	4·44	13·9	5·36	9·8	4·04	12
	IV ..	12·7	4·60	14·7	5·22	10·6	3·89	8
9 months	I ..	12·0	4·41	14·0	5·62	8·4	3·61	7
	II ..	12·0	4·43	13·6	4·88	10·5	3·69	6
	III ..	12·9	4·53	14·1	5·56	11·5	3·68	8
	IV ..	12·3	4·49	12·9	5·26	11·9	3·98	4
1 year	I ..	12·0	4·15	14·0	5·00	11·2	3·40	4
	II ..	12·7	4·06	13·4	4·15	11·5	3·97	3
	III ..	11·9	4·51	12·6	4·77	11·5	4·23	5
	IV ..	12·6	4·04	13·0	4·38	12·0	3·41	3

Group I. Controls.
II. Cob. Sulph. 10 mg., 1-12 days.
III. Cob. Sulph. 20 mg., 4-8 weeks.
IV. Cob. Sulph. 20 mg. plus Fe. Sulph g. 4½, 4-8 weeks.

indications for additional cobalt therapy. All these were controls. A fourth control (P.S.) with a count of 66% haemoglobin and 3·08 m./c.mm. red cells at 5 months had severe symptoms of anaemia with anorexia, lassitude, and extreme pallor, and it was decided to treat this infant, although the count had not reached our minimum criteria. The initial counts and response to treatment of these four cases are shown in Table 8. All infants responded satisfactorily to treatment but the two cases which did not require therapy until the age of 5 months were obviously suffering from coincidental iron deficiency, and required iron as well as cobalt before satisfactory haemoglobin levels could be reached although the red cells responded to cobalt alone.

In 14 cases the haemoglobin fell to levels requiring iron therapy. These were divided as follows: Group I, 8 cases; Group II, 3 cases; Group III, 3 cases; Group IV, nil cases.

Details of these cases are shown in Table 10. The youngest infant requiring iron was 4 months, and eight of the 14 cases required treatment at 6 months. This appeared to be the most common time for an iron deficiency anaemia to become manifest in our series. Two of the three Group III cases requiring iron were twins, and six of the total 14 cases requiring iron were twins.

No case receiving iron and cobalt from 4 to 8 weeks required additional iron therapy. The numbers in the various groups were approximately the same and we feel it is of some significance that all infants requiring additional cobalt were controls and that 57% of the cases requiring additional iron were also controls. The role of cobalt in favouring iron utilization has been mentioned before and will be reviewed in relation to these results in the discussion.

It has been shown (Mackay, 1931) that artificially fed infants are more prone to anaemia than those receiving breast milk, and that if anaemia develops

TABLE 3

AVERAGE HAEMOGLOBIN CONTENT AND RED CELL COUNTS FROM BIRTH TO 1 YEAR IN INFANTS OF BIRTH WEIGHT UNDER 4½ LB.

Age and Group		Average Counts		Maximum Counts		Minimum Counts		No. of Cases
		Hb. (%)	R.B.C. (m.)	Hb. (%)	R.B.C. (m.)	Hb. (%)	R.B.C. (m.)	
Birth	I ..	21·3	5·70	24·9	7·38	15·3	4·10	22
	II ..	20·7	5·52	22·4	6·58	15·7	5·12	6
	III ..	20·4	5·45	25·2	6·32	15·4	3·92	15
	IV ..	21·7	5·47	24·5	6·50	17·5	4·60	10
1 month	I ..	14·6	3·82	19·2	4·96	11·1	2·90	17
	II ..	13·3	4·16	15·7	4·68	11·9	3·52	6
	III ..	14·7	3·99	19·6	5·36	10·9	2·84	15
	IV ..	14·7	4·02	17·2	5·42	11·2	2·35	10
2 months	I ..	10·6	3·03	13·2	3·98	8·5	2·15	13
	II ..	11·3	3·71	13·0	4·38	10·5	2·92	5
	III ..	12·7	4·14	15·7	5·72	10·2	3·14	15
	IV ..	11·8	3·72	12·6	4·92	9·8	3·19	10
3 months	I ..	10·8	3·41	14·0	4·10	9·1	2·80	11
	II ..	10·0	3·41	12·6	4·00	8·8	2·87	4
	III ..	12·2	4·11	14·8	5·12	9·8	3·58	12
	IV ..	11·9	3·82	14·0	4·56	9·7	3·18	10
4 months	I ..	10·8	3·63	12·2	4·46	9·2	2·88	10
	II ..	11·1	3·80	12·6	4·42	10·2	3·36	4
	III ..	11·6	4·32	14·0	5·20	8·7	3·48	14
	IV ..	12·5	4·37	14·4	5·62	10·5	3·32	10
5 months	I ..	10·2	3·73	11·9	4·42	7·3	2·58	9
	II ..	10·4	3·83	12·6	4·20	8·0	3·46	4
	III ..	11·2	4·26	13·0	5·02	8·5	3·66	13
	IV ..	12·6	4·67	14·0	6·14	10·6	3·50	10
6 months	I ..	11·3	4·19	13·3	4·96	9·0	3·45	10
	II ..	11·9	4·03	12·6	4·26	11·2	3·92	3
	III ..	11·5	4·73	13·3	6·40	10·0	3·96	11
	IV ..	12·9	4·56	14·7	5·27	10·5	4·00	10
9 months	I ..	12·6	4·37	13·3	4·70	11·9	3·98	3
	II ..	12·7	3·94	12·9	4·88	12·6	3·01	2
	III ..	12·0	4·66	15·7	5·32	10·0	4·16	7
	IV ..	12·0	4·76	13·6	5·06	10·5	4·42	6
1 year	I ..	12·6	4·09	—	—	—	—	1
	II ..	12·9	4·25	14·7	5·00	11·2	3·50	2
	III ..	13·0	4·44	15·4	5·07	11·9	4·10	3
	IV ..	13·3	4·44	—	—	—	—	1

TABLE 4

AVERAGE HAEMOGLOBIN CONTENT AND RED CELL COUNTS FROM BIRTH TO 1 YEAR IN INFANTS OF EIGHT TO NINE MONTHS' GESTATION

Age and Group		Average Counts		Maximum Counts		Minimum Counts		No. of Cases
		Hb. (%)	R.B.C. (m.)	Hb. (%)	R.B.C. (m.)	Hb. (%)	R.B.C. (m.)	
Birth	I ..	21·8	5·82	25·2	7·38	15·7	4·58	30
	II ..	22·3	6·10	22·4	6·98	15·7	4·42	12
	III ..	20·2	6·10	25·2	7·20	18·2	5·16	12
	IV ..	22·0	6·12	25·2	7·12	17·6	5·68	8
1 month	I ..	13·9	4·14	17·6	5·50	10·6	2·92	17
	II ..	14·7	4·39	18·9	5·74	10·9	2·59	12
	III ..	13·4	4·20	16·0	5·76	11·1	2·84	12
	IV ..	15·0	4·04	17·1	4·54	13·2	3·16	8
2 months	I ..	10·9	3·54	12·6	4·36	9·5	2·64	14
	II ..	11·6	3·75	16·1	4·50	9·2	3·24	11
	III ..	12·5	4·14	14·1	4·78	10·6	3·40	12
	IV ..	12·6	4·41	16·0	5·90	11·2	3·58	8
3 months	I ..	10·8	3·75	12·6	4·48	9·2	2·84	13
	II ..	10·8	3·60	14·8	4·34	8·8	2·87	11
	III ..	11·8	4·44	13·3	5·56	9·8	3·58	11
	IV ..	11·9	4·34	12·5	5·00	11·2	3·76	6
4 months	I ..	11·1	3·72	12·6	4·70	8·4	2·59	13
	II ..	11·5	4·15	15·4	5·02	9·2	3·44	11
	III ..	11·8	4·30	14·0	5·48	8·7	3·56	12
	IV ..	12·6	4·19	14·6	4·76	11·9	3·66	6
5 months	I ..	11·1	3·99	13·3	4·98	7·3	2·58	12
	II ..	11·5	4·38	15·0	4·92	8·0	3·46	11
	III ..	11·8	4·39	13·3	5·50	8·8	3·95	11
	IV ..	11·9	4·12	12·3	4·74	11·5	3·58	5
6 months	I ..	11·6	4·24	13·3	4·96	8·0	3·48	10
	II ..	11·6	4·29	14·0	4·79	9·2	3·66	8
	III ..	11·8	4·54	13·9	6·40	9·8	3·96	10
	IV ..	12·0	4·62	12·9	5·10	10·6	4·10	4
9 months	I ..	12·9	4·63	14·0	5·62	10·9	4·03	6
	II ..	12·5	4·00	13·6	4·72	10·5	3·01	5
	III ..	12·9	4·58	14·0	5·56	11·2	3·68	7
	IV ..	12·0	4·62	12·3	5·26	11·9	3·98	2
1 year	I ..	12·2	4·25	14·0	5·00	11·2	3·40	3
	II ..	12·3	3·82	13·4	4·15	11·2	3·50	2
	III ..	11·8	4·45	12·6	4·77	11·2	4·16	5
	IV ..	12·9	4·33	—	—	—	—	1

it is more severe in the artificially fed. The incidence of breast feeding in our series is shown in Table 10. Any infant breast fed for five months or longer without regular complements was considered as fully breast fed. Partial breast feeding included cases fed for any period over one month and infants who received breast milk together with more than occasional complements. Any infant on the breast for less than one month was classified as 'never breast fed'. Consideration of Table 10 makes it clear that the higher blood levels obtained in the treated cases was in no way due to breast feeding as the incidence of breast feeding was considerably higher in the control group than in any other. The cases for each group were selected at birth before feeding had begun at all, and we cannot explain this difference in feeding methods which appears to be entirely fortuitous.

In view of the conflicting evidence about the effect of cobalt on appetite and weight gain in both animals and man, the weights of all infants were recorded at each attendance. The average weight gain in ounces over birth weight at 2, 4 and 6 months of age are shown in Table 10, together with the average birth weight of each group. The birth weights in the four groups were comparable and the differences in weight gain are not significant. At 2 months all infants had finished cobalt treatment and this therefore seemed a suitable time to start comparisons.

There was no evidence of toxicity in any case under treatment; appetite and vigour were good and the preparation was readily taken in water or milk. There is nothing to suggest that cobalt in any way impairs the general progress or rate of weight gain in premature infants in the dosage employed.

In the cases which developed anaemia symptoms were confined to pallor except in the baby already

TABLE 5

AVERAGE HAEMOGLOBIN CONTENT AND RED CELL COUNTS FROM BIRTH TO 1 YEAR IN INFANTS OF SIX TO EIGHT MONTHS' GESTATION

Age and Group		Average Counts		Maximum Counts		Minimum Counts		No. of Cases
		Hb. (%)	R.B.C. (m.)	Hb. (%)	R.B.C. (m.)	Hb. (%)	R.B.C. (m.)	
Birth	I ..	21·4	5·71	25·2	7·20	15·3	4·10	23
	II ..	20·6	5·83	24·5	6·60	15·7	5·12	10
	III ..	20·6	5·35	25·2	6·80	14·3	3·92	17
	IV ..	21·4	5·21	24·5	6·50	16·8	4·60	14
1 month	I ..	14·7	3·85	19·2	4·96	10·6	2·90	18
	II ..	15·0	4·46	18·2	5·36	11·9	3·98	8
	III ..	14·3	3·89	19·6	5·36	8·8	2·62	17
	IV ..	14·8	4·00	18·7	5·42	11·2	3·35	14
2 months	I ..	10·6	3·06	13·2	3·98	8·5	2·15	14
	II ..	12·3	3·85	13·3	4·82	10·5	2·92	7
	III ..	12·5	4·13	17·5	5·32	9·8	3·14	17
	IV ..	12·2	3·83	15·4	4·92	9·8	3·19	14
3 months	I ..	10·8	3·40	14·0	4·10	9·1	2·68	11
	II ..	11·2	3·81	12·6	4·00	9·8	3·62	4
	III ..	12·0	4·20	14·8	5·14	9·0	3·60	15
	IV ..	12·2	4·01	14·1	5·70	9·7	3·18	14
4 months	I ..	10·6	3·60	12·2	4·46	9·2	2·88	10
	II ..	11·2	4·09	12·6	4·42	10·2	3·36	4
	III ..	11·5	4·30	13·7	5·08	7·4	3·48	16
	IV ..	12·6	4·41	14·4	5·62	10·5	3·32	14
5 months	I ..	10·4	3·71	11·9	4·44	9·2	3·10	9
	II ..	11·8	4·06	12·9	4·34	9·8	3·80	4
	III ..	11·5	4·39	13·9	5·24	9·8	3·66	13
	IV ..	12·7	4·52	14·0	6·14	10·6	3·50	14
6 months	I ..	10·9	4·13	13·3	4·84	9·0	3·45	11
	II ..	12·2	4·22	12·6	4·74	11·9	3·92	4
	III ..	11·6	4·60	13·9	5·36	10·0	3·96	13
	IV ..	13·0	4·57	14·7	5·27	10·5	3·89	14
9 months	I ..	11·2	4·05	12·6	4·70	8·4	3·61	4
	II ..	11·9	4·83	12·9	4·88	11·5	4·74	3
	III ..	12·3	4·60	15·7	5·32	10·0	3·91	8
	IV ..	12·3	4·66	13·6	5·06	10·5	4·06	8
1 year	I ..	12·2	3·96	12·6	4·09	11·9	3·84	2
	II ..	13·2	4·34	14·7	5·00	11·5	3·97	3
	III ..	13·3	4·53	15·4	5·07	11·9	4·10	3
	IV ..	12·7	4·07	13·3	4·44	11·6	3·41	3

mentioned (P.S.) who was treated with cobalt at 5 months. However, after treatment with iron or cobalt, the mothers of these anaemic infants frequently stated spontaneously that the children were much improved, with increased appetite and vigour. It seems possible, therefore, that even if anaemia in premature infants does not usually produce marked symptoms, there is a subclinical debility which becomes more evident in retrospect.

Discussion

Our average values for control cases do not show a very severe anaemia, reaching lowest values of 10·8 g. haemoglobin, and 3·75 m. red cells at 3 months of age for infants of eight to nine months' gestation, and 10·6 g. haemoglobin and 3·06 m. red cells at 2 months for those of six to eight months' gestation. These figures are, however, well below those given by Herz (1928) as indicative of anaemia. The subsequent satisfactory increases and the relatively few cases requiring iron therapy are, we feel, partly due to the early introduction of a mixed diet with a liberal supply of iron-containing foods, and partly to the continuous supervision by one team employing the same feeding methods. This meant that mothers could follow a regular plan and had a feeling of security where diet was concerned, a factor missing if feeding advice is obtained from several sources.

It is a significant fact that none of the Group IV cases receiving iron as well as cobalt required additional iron therapy and that the haemoglobin levels of this group remained consistently and significantly higher than those in any other group after the age of 4 months. No attempt is made in this paper to determine the exact mechanism of cobalt in stimulating erythropoiesis but it would appear that its action is in part due to a favourable influence on the utilization of available iron for blood synthesis. The Group III infants who developed

TABLE 6

STATISTICAL ANALYSIS OF AVERAGE HAEMOGLOBIN CONTENT OF BLOOD TO 6 MONTHS* OF AGE

Group	No. of Cases		Age in Months						
	1 month	6 months	Birth	1	2	3	4	5	6
I ..	35	21	21·75	14·40	10·78	10·78	10·93	10·93	11·35
II ..	20	12	21·50	15·10	†11·81	10·97	11·61	11·66	11·83
III ..	29	23	20·80	14·08	12·64	12·02	11·72	11·64	11·78
IV ..	22	18	21·67	14·99	12·40	12·14	†12·69	†12·55	†12·87
I and II combined	55	33	21·67	14·66	11·18	10·85	11·20	11·24	11·52
III and IV combined	51	41	21·18	14·47	†12·54	†12·07	†12·13	†12·03	†12·26

* Cases grouped irrespective of birth weight or gestation period.

† The difference between this pair of means is significant at the 5% level.

TABLE 7

STATISTICAL ANALYSIS OF AVERAGE RED CELL COUNTS TO 6 MONTHS* OF AGE

Group	No. of Cases		Age in Months						
	1 month	6 months	Birth	1	2	3	4	5	6
I ..	35	21	5·76	3·96	3·34	3·57	3·70	3·91	4·19
II ..	20	12	5·98	†4·42	†3·79	3·66	†4·17	†4·30	4·27
III ..	29	23	5·67	4·01	4·14	4·32	4·30	4·39	4·59
IV ..	22	18	5·78	4·08	4·04	4·11	4·36	4·46	4·58
I and II combined	55	33	5·82	4·13	3·52	3·60	3·89	4·07	4·22
III and IV combined	51	41	5·72	4·04	†4·10	†4·23	†4·33	†4·42	†84·9

* Cases grouped irrespective of birth weight or gestation period.

† The difference between this pair of means is significant at the 5% level.

an iron deficiency anaemia were presumably lacking in endogenous iron or had a poor absorption. Two of the three cases requiring iron in this group were twins and this may account for their low iron content. We agree with Waltner (1930) and Virdis (1952) that iron should be given together with cobalt to obtain the most satisfactory results. Although no group of cases received cobalt after the end of the second month, it appears from our results that this substance may be stored in the body and utilized when needed. All three infants who received cobalt from 4 to 8 weeks but subsequently developed an iron deficiency anaemia had adequate red cell counts, and this suggests that direct stimulation of the erythroid tissue of the marrow is also a factor in the haemopoietic action of cobalt. The effect of cobalt on the marrow requires further elucidation and this aspect of its action is now being investigated.

Animal studies with radioactive cobalt have shown that young animals absorb more than adult animals and that they have higher blood levels after oral administration (Comar and Davis, 1947). The liver appears to be the principal storage organ, though in animals relatively little is retained, about 5% of an intravenous dose after 10 days in cattle (Comar, Davis and Taylor, 1946). It is not known whether these results are applicable to man, but in any case it is probable that only extremely small amounts are necessary to produce a haemopoietic effect. The detectable dose of cobalt which will produce polycythaemia in rats is 0·15 mg. daily, and 2 mg. per kg. body weight is capable of causing polycythaemia in dogs (Frost *et al.*, 1941). Our dosage in this series has been arbitrary and based on the existing reports of the therapeutic use of cobalt in man together with the doses used to produce polycythaemia in animals. It is possible that more prolonged treatment would

TABLE 8

DATA FOR CASES ON THERAPEUTIC COBALT

Name and Birth Weight	Prematurity in Weeks	Age Cobalt Started	Duration of Therapy	Hb. (%)		R.B.C. (m.)	
				Before	After	Before	After
R.W. 3.10. Twin ..	5	2 months	1 month	65	86	2·15	4·32
J.B. 3.15. Twin* ..	3	5 months	2 months	52	70	2·58	4·70
A.Q. 4 lb. Twin ..	4	2 months	1 month	69	79	2·48	3·58
P.S. 4.9	2	5 months	1 month	66	60	3·08	4·16

All cases controls. Dosage 20 mg. daily.

* Plus iron for second month of treatment.

TABLE 9

DATA FOR CASES REQUIRING IRON

Name and Birth Weight	Prematurity in Weeks	Group	Age Iron Started	Duration of Therapy	Hb. (%)		R.B.C. (m.)	
					Before	After	Before	After
J.B. 3.15.* Twin	3	I	6 months	4 months	55	89	4·24	4·98
P.S. 4.9*	2	I	6 months	did not attend	60	did not attend	4·16	did not attend
J.A. 4.0	7	I	6 months	3 months	74	100	4·84	4·46
S.T. 3.15. Twin	7	I	6 months	2 months	74	88	3·84	4·06
A.K. 4.13	Term	I	6 months	3 months	71	90	4·18	4·80
G.A. 4.12. Twin	2	I	6 months	3 months	57	90	3·48	4·50
K.B. 4.1	8	I	6 months	5 months	64	69	3·92	4·32
M.C. 5.4	5	I	9 months	did not attend	60	did not attend	3·94	did not attend
R.F. 5.3	Term	II	5 months	7 months	69	64	4·92	4·45
P.B. 3.13. Twin	3	II	5 months	5 months	57	82	3·46	5·12
A.A. 4.10	2	II	6 months	did not attend	66	did not attend	4·24	did not attend
P.B. 4.12. Twin	7	III	4 months	2 months	53	70	3·65	3·77
M.O'D. 3.13. Twin	7	III	9 months	2 months	72	95	4·22	5·08
N.S. 4.3	Term	III	5 months	5 months	63	80	4·00	4·70

* After one month of cobalt.

TABLE 10

INCIDENCE OF BREAST FEEDING AND AVERAGE GAIN OVER BIRTH WEIGHT AT 2, 4 AND 6 MONTHS

Group	Number of Infants	Breast Fed (%)			Average B.W.	Average Gain over B.W. (oz.)		
		Fully	Partly	Never		2 Months	4 Months	6 Months
I ..	21	53·8	38·6	7·6	4·11	57·0	118·4	169·2
II ..	15	36·8	36·8	26·4	4·7	61·9	117·5	173·9
III ..	28	31·2	46·9	21·9	4·7	57·7	114·7	160·8
IV ..	21	25·9	48·2	25·9	4·10	47·0	104·1	156·3
I and II ..	36	—	—	—	4·9	59·1	118·0	171·1
III and IV ..	49	—	—	—	4·8½	53·1	110·1	158·9

be of greater benefit and we feel that more work is needed before the role of cobalt in the prevention of the anaemia of prematurity can be fully defined.

Summary and Conclusions

The experimental literature of cobalt as a haemopoietic agent is briefly summarized, and a more detailed review is given of its use in the treatment of anaemia in man.

One hundred and twenty-six premature infants were divided into four groups. Eighty-three were followed up six months or longer. Group I acted as controls. Group II received cobalt sulphate, 10 mg. daily, from one to 12 days. Group III received cobalt sulphate, 20 mg. daily, from four to eight weeks. Group IV received cobalt sulphate, 20 mg., and ferrous sulphate, gr. $4\frac{1}{2}$ daily, from four to eight weeks.

Cobalt appears to be of value in the prevention of the early anaemia of premature infants, and if iron is administered simultaneously the risk of an iron deficiency anaemia developing from the fourth month onwards is considerably reduced. Cobalt has no toxic effects and no unfavourable influence on the weight gain in the dosage employed. The mode of action is uncertain but two possibilities seem likely: (1) a direct action on the erythropoietic tissue in the marrow; (2) a possible catalytic action enabling available iron to be more readily utilized for haemoblobin synthesis.

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CONGENITAL ECTROPION OF THE UPPER LIDS

BY

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This report of a case of congenital ectropion is presented not only because of its intrinsic interest and great rarity but also because, so far as one has been able to determine, it is the first case in which an attempt has been made to elucidate the aetiology of the condition by a detailed examination of the lids.

Collins (1915) reported a case of a girl aged 4 months who had bilateral partial ptosis, well marked epicanthus and ectropion of the lower lids. The defect in the eyelids was stated to have been present from birth. The lower lacrymal puncta on each side were present but they stood away from the eyeballs. She was able to use the orbicularis muscles to close her eyes and to screw up her lids. In that case 'a wedge-shaped piece of the whole thickness of the right lower lid was cut out a little way internal to the outer canthus. The base of the wedge was at the free margin of the lid and measured about six millimetres in length. A stitch was inserted through the two raw surfaces left, just inside the line of the lashes, and by means of it they were drawn together and united'. The length of the lower lid was thus shortened and drawn up into a better position. Microscopical examination of sections of the lower lid showed a well-developed orbicularis muscle.

Mackay (1915) described a similar case but with the distinction that in addition to bilateral eversion of the lower lids there was microphthalmos in both eyes and symmetrical coloboma iridum and a deep-seated cyst below the left lower lid.

Von Herrenschwand (1916) reported a case of a man aged 48 years who had bilateral ectropion of the upper and lower eyelids since birth. In that case, even without the patient's history that the condition had been present since birth, attention would have been drawn to a congenital anomaly by the absence of the puncta lacrimalia, and by the presence in each eye of a symmetrically situated conjunctival fold which originated from the fundus of the conjunctival sac, and which was inserted in a pinguecular-like thickening encroaching slightly on to the outer limbus of the cornea just below a horizontal meridian.

Gordon and Cragg (1944) reported a case of mild congenital ectropion of all four lids, associated with ptosis of the upper lids. Their patient was a man aged 23 years. He had six brothers and three sisters, of whom two brothers and one sister had a similar but less marked defect. The father of that family was stated to have had a defect of the same nature.

Photographs of the four cases mentioned above show that they do not bear a close resemblance to the picture presented by our case and an exhaustive search of the world literature has revealed only two cases similar to the case reported here.

Erb (1909) described a case of bilateral congenital ectropion of the upper eyelids in a 2-day-old infant. The father said the changes were seen immediately after birth and that they had increased since birth.

Mertens (1920) also reported a case in which there was complete eversion of both upper lids immediately after birth. The mother, a healthy woman aged 42 years, was a seventh para with a generally contracted flat pelvis. All previous births had been difficult, and in all, labour had been prolonged. The ectropion was treated with boric acid and vaseline dressings and eventually completely disappeared but 'there persisted a narrowing of the palpebral fissure especially in the inner canthus and the palpebral fissures were oblique from upper outer towards lower inner angles'. This description, and the photograph of the child, strongly suggest that the case was a mongol, though this possibility was not put forward by Mertens. The child died with convulsions at the age of 4 months.

Case Report

The patient, a boy weighing 7 lb. 12 oz. at birth, was the seventh child of a mother aged 35 years. Previous pregnancies had resulted in the birth at full term of infants whose birth weights ranged from 8 lb. to 12 lb. At no birth had labour been difficult and all the other children were normal except the sixth, who was a stillborn foetus with hydrocephalus and a cervical meningocoele.

In the present pregnancy the mother's health was good until the seventh month when she developed signs of mild pre-eclamptic toxaemia. Labour, which lasted six hours, had not been difficult and the child was born, vertex presenting, without the aid of forceps.

Immediately the head appeared at birth both upper lids were seen to be completely everted, and the whole inner surface of the upper lids and a large part of each upper transitional fold lay exposed. The transitional folds were so swollen that the lid opening was completely obliterated. The ectropion appeared as large oedematous swellings covered by a blue-red mucosa. When the child cried the swellings increased in size and the colour became slightly more bluish. The lower lids appeared normal and the eyes, which were seen only with great difficulty on retraction of the lower lids, appeared smaller than normal.

The infant (Fig. 1) had the characteristic stigmata of

FIG. 1.—Large oedematous swelling on each upper lid.

mongolism. The epicanthic fold of skin at the inner canthus was strongly developed and the nose was stubbed. The cranium was devoid of eminences and the occiput flattened. The conjunctival swellings of the upper lids obscured the obliquity of the palpebral fissures but on close inspection it was seen that each outer angle pointed upwards. The tongue was frequently protruded. The palms and soles showed the markings considered to indicate mongolism.

There was no evidence of any birth trauma.

The skin was normal.

A few days after birth the conjunctival swellings became less intense but the ectropion persisted and there was minimal sloughing of the central area of the oedematous swelling on each eye.

On the eighth day of life, under general anaesthesia, the excess tissue beneath the right upper eyelid was excised and the two raw conjunctival margins united by a continuous suture.

The day following the operation the infant had an attack of cyanosis and died suddenly.

Necropsy Report. There was no obvious infection of the operation site. The foramen ovale was widely patent and the mitral valve showed a few little nodular thickenings of the free margin but there was no developmental anomaly of the heart.

The right lung was swollen and felt heavy. The pleura was dark red and dotted with small haemorrhages. On section the consistency was fairly firm especially in the lower lobe. The left lung contained more air and was only moderately congested.

The right kidney showed foetal lobulation. There was a dark red area at the lower pole involving about one-third of the surface and on section there was a haemorrhagic infarct extending to the pelvis. The affected cortex was pale in its inner third. No frank thrombi were seen in the vessels at the hilum.

The left kidney appeared normal.

The brain was congested and very soft. There was no thrombosis of the sinuses and no evidence of meningitis. The body cavities were normal. The liver, spleen, adrenals, bladder, prostate, testicles, oesophagus, small and large intestine, pancreas, thymus, trachea and pituitary were all normal.

Histology. The lungs were extremely congested and there were multiple large intra-alveolar haemorrhages. On the margins of the haemorrhages the alveoli contained oedema fluid and a few large mononuclears but there was no acute inflammatory reaction.

In the kidneys the haemorrhagic area was seen to be a recent infarct. The capsular tissues were oedematous and congested and a narrow subcapsular zone of tissue had survived. The cortex deep to this showed necrosis with nuclear disintegration and a mild inflammatory reaction. The lesion extended partly to the medulla. The blood vessels were congested but no emboli were seen in the arteries, nor thrombi in the veins. The other kidney was much congested but not necrotic.

The liver showed marked congestion and fairly diffuse fatty vacuolation of the liver cells. The portal tracts were normal.

The eyes, on sectioning, showed normal structure and position of the various intra-ocular tissues.

Other organs were normal histologically.

Detailed Report on the Eyelids. After removal of the eyeballs the eyelids were excised by a circular cut around the orbital margins so as to include the full thickness of the lids and as much of the conjunctival tissues as remained in the orbit. The earlier removal of the eyeballs had deranged the lid margins somewhat and the lids were fragmented during preparation. It was thus impossible to estimate precisely the relative amounts of collagenous tissue forming the upper tarsal plates. The lower lids were in a good state of preservation apart from the loss

of continuity with the inferior rectus and of the reflection of the conjunctiva on to the eyeball.

Comparison was made with sagittal midline sections of the lids and eyeballs of a 35-week male foetus. In so far as the material allowed of comparison, the absolute and relative thicknesses of the various components of the lids were measured at a distance of 2 mm. from the free margins of the lids, and the absolute as well as the relative values of the components compared.

There was no appreciable difference in the absolute thickness of the subconjunctival collagen layer, of the thickness of the meibomian glands, of the ratio of thickness of collagen to that of gland or of thickness of orbicularis palpebrarum muscle to thickness of lid, between the control and the lower lids of the specimen. It was not possible to measure these constituents of the upper lids of the specimen but a firm impression was formed that the amounts of muscle, gland and collagen were comparable to the control.

RIGHT UPPER LID (Operated Side). The lid margin was torn and the meibomian glands almost gone. There was a well marked notch on the inner aspect of the lid at the site of operative removal of tissue, only skin and subcutaneous collagen remaining.

LEFT UPPER LID (Non-Operated Side). The lid margin was torn and the continuity of skin and conjunctiva was lost. The meibomian glands were well developed and embedded in collagen tissue of approximately normal amount. The orbicularis muscle was well developed but the insertion of the levator palpebrae superioris and superior rectus tendons into the lid could not be compared with the normal owing to prior removal of the eyeball.

RIGHT LOWER LID (Operated Side). Well developed meibomian glands were embedded in collagen. The lid was thinner and more elongated than the control, but this could easily be accounted for by the removal of the eyeball before fixation.

LEFT LOWER LID (Non-operated Side). The lid was rather thicker and less elongated, and its general condition less deranged than that of the right lid. Otherwise there was no significant difference.

Table 1 gives the lengths in units, as measured by a micrometer eyepiece, of structures of the right lower lid, left lower lid and a control lower lid.

TABLE 1

STRUCTURES OF THE AFFECTED LOWER LIDS COMPARED WITH A CONTROL

Lengths Units Measured by Micrometer Eyepiece	Right Lower Lid	Left Lower Lid	Control Lower Lid
Length of meibomian glands ..	36	21	19
Thickness of meibomian glands	4	5	5·5
Thickness of subconjunctival collagen layer	1·5	1·5	1·5
Thickness of lid	10	13	26
Thickness of muscle layer ..	3	4·5	10
Ratio of collagen: lid	1·5/10	1·5/13	1·5/26
collagen: gland ..	1·5/4	1·5/5	1·5/5·5
muscle : gland ..	3/10	4·5/13	5/13

The low proportion of collagen to lid thickness in the ectropic lids as compared with the control is probably not significant, as the control lids were fixed when *in situ* and before they had been touched in any way, whereas the lids of the specimen were disturbed before fixation.

It can be concluded that there did not appear to be any significant difference in the amount of collagen forming the tarsal plates, or of the amount of meibomian gland tissue embedded in that collagen, between the lower lids of a case of congenital ectropion of the upper lids and a normal baby. While it was not possible to reach such a definite conclusion concerning the composition of the upper lids in this case of ectropion, it appears to be extremely probable that there was no significant deficiency in the amounts of collagen present there either.

Discussion

Acute or spastic ectropion may occur in children in the first few years of life and is then associated with diseases of the eye which cause inflammatory swelling and blepharospasm. If the conjunctiva protrudes as a large swelling it becomes strangulated at its base by the lid margin. The venous return is thus obstructed, causing a further increase in the conjunctival swelling, and if this increases still further the lid may become everted as the result of the pressure exerted by the oedematous conjunctiva. Once the lid is everted the peripheral bundles of the palpebral portion of the orbicularis oculi contract around the tarsal plate and maintain the lid in the everted position. The venous congestion thus produced gives the blue-red appearance to the everted lids. In all such cases of infantile ectropion the initiating factor is a disease of the eyes leading to blepharospasm or spasm of the orbicularis oculi.

In our case, however, the eyes were healthy and some mechanism other than spasm must have been involved.

As the ectropion was present on the appearance of the head at birth, birth trauma or a mechanical cause acting *in utero* have to be considered. Labour was not difficult, and as there was no evidence of birth trauma, it seems reasonable to exclude trauma as an initiating factor, especially as the mother had had six previous children, all of whom had been of upper average weight at birth and none of whom showed any abnormality of the lids.

In the case described by Erb the upper lids were large and flaccid. Erb thought this was an aetiological factor in the causation of the condition and that the ultimate cause was a long-lasting and difficult labour with a breech presentation. He postulated that as the head passed through the birth canal the lids were turned upwards and everted and that spasm of the lids might have been an additional factor which, at any rate, prevented

spontaneous reposition and favoured oedematous swelling of the lids. However, in our case the lids were normal in size, and the birth was a left occipito-anterior presentation with an easy delivery, so that none of the factors assumed to be of importance in Erb's case operated.

The detailed histological examination may be accepted as excluding any intrinsic defect of the lids as a cause of the ectropion.

A striking feature of our case was the marked over-development of the epicanthic folds which pressed on the outer surface of each upper lid in the region of the inner canthus. It is suggested that the constricting effect so produced hindered the venous return from the upper lids and caused an oedematous swelling of the conjunctiva and that the swollen conjunctiva then exerted pressure on the lids and caused them to become everted.

As the case described by Mertens was very probably also a mongol it is likely that a similar mechanism was at work in that case, though a difficult labour may have been an aggravating factor.

If this theory is accepted the rational treatment of the condition would be to make a V-shaped incision in each epicanthic fold with the open end of the V towards the free margin. This would ease the pressure on the lids and so relieve the oedema of the conjunctiva and allow reposition of the lid.

Summary

A case of congenital ectropion of the upper lids in a mongol infant is described.

The theory is put forward that the over-development of the epicanthic fold is the initiating factor in the condition.

A rational treatment is suggested.

I am indebted to Professor F. M. B. Allen, Dr. Muriel J. L. Frazer and Mr. David H. Craig for advice and helpful criticism.

The case was under the care of Dr. Muriel J. L. Frazer to whom I am grateful for encouragement and permission to publish.

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CONGENITAL STRIDOR CAUSED BY AN ABERRANT PULMONARY ARTERY

BY

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That congenital stridor can be caused by vascular abnormalities has become more widely known during the past few years. With this increased awareness, the list of anomalies known to be capable of causing respiratory embarrassment has lengthened. The following case is, as far as we are aware, the first one due to an aberrant pulmonary artery to be described.

Case Report

The patient was a boy, the youngest of three children, the others having had no relevant illnesses. He was delivered normally at term. During the first two weeks after birth he had been well, but then developed a wheeziness which was constantly present although varying in intensity. This variation bore no relation to feeding, and he did not regurgitate his feeds. He was admitted to another hospital at the age of 4 months with an acute respiratory infection diagnosed as tracheo-bronchitis. This resolved within a week, but the child remained wheezy.

At the age of 5 months he was admitted to Ruchill Hospital having developed another attack of acute respiratory distress during the preceding 24 hours. There was marked stridor with indrawing of the lower intercostal spaces and supraclavicular fossae. Expiratory wheezing was more marked than inspiratory. Percussion of the chest was normal. On auscultation, coarse crepitations were heard throughout both lungs. The lungs were clear radiologically. Acute tracheo-bronchitis was diagnosed. He was placed in a steam tent and treatment with aureomycin, 50 mg. every six hours, was begun. The temperature, which had been 101·2° F. on admission, was normal within 24 hours, and the child's condition was sufficiently improved within 48 hours for him to be removed from the steam tent. On the sixth day aureomycin was discontinued. The child by then was fairly lively. He had shown no reluctance to feed, and no exacerbation of his symptoms was associated with feeding. Wheeziness, however, remained but was now confined to expiration. During sleep it was almost inaudible.

The history was, of course, suggestive of an anomaly of the great vessels causing compression of the trachea. When the child was sufficiently well, investigations were begun. Laryngoscopy was normal. No narrowing of the trachea could be seen radiologically on the postero-anterior and lateral views of the chest, but the trachea was not outlined with iodized oil for fear of precipitating a further acute respiratory infection. Unfortunately, as the child would not cooperate, it was difficult to get satisfactory radiographs of the barium-outlined oesophagus. The films obtained excluded gross compression or deviation but were not of sufficient quality to show minor indentations. Further examination was about to be made but was prevented by the child's developing a recurrence of the illness which had originally led to his admission. He was then 6 months old. He was seen by Mr. R. S. Barclay and transferred to the Thoracic Surgical Unit at Mearnskirk Hospital. The diagnosis of a vascular anomaly had not yet been established but the

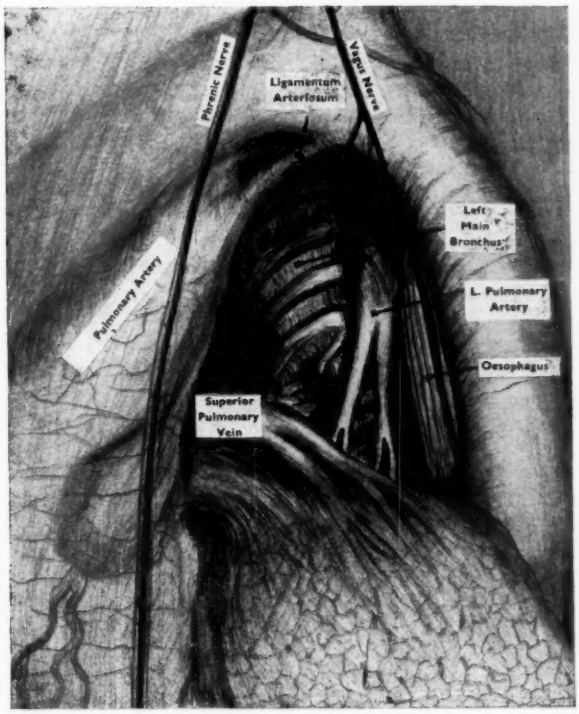

FIG. 1.—Drawing showing the appearances of the left hilum at operation.

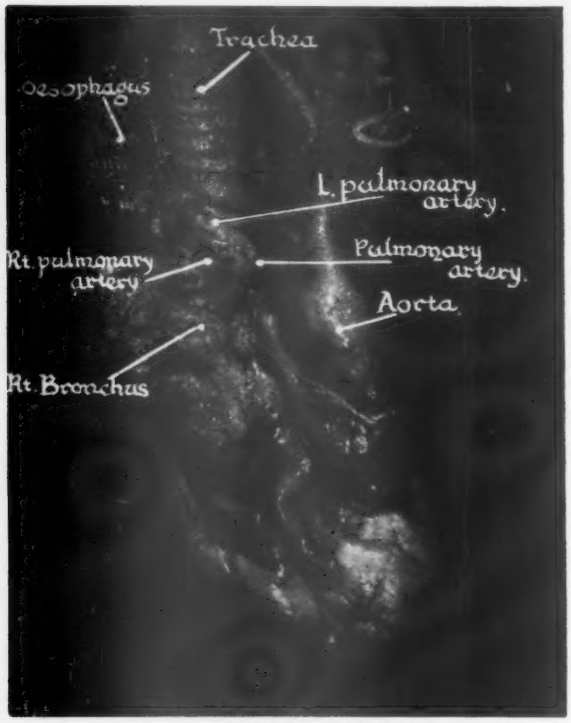

FIG. 2.—Right lateral view of the dissected necropsy specimen. It shows the main pulmonary artery passing to the right of the trachea. The right branch is given off and lies above the right main bronchus. The left branch then passes between the trachea and the oesophagus.

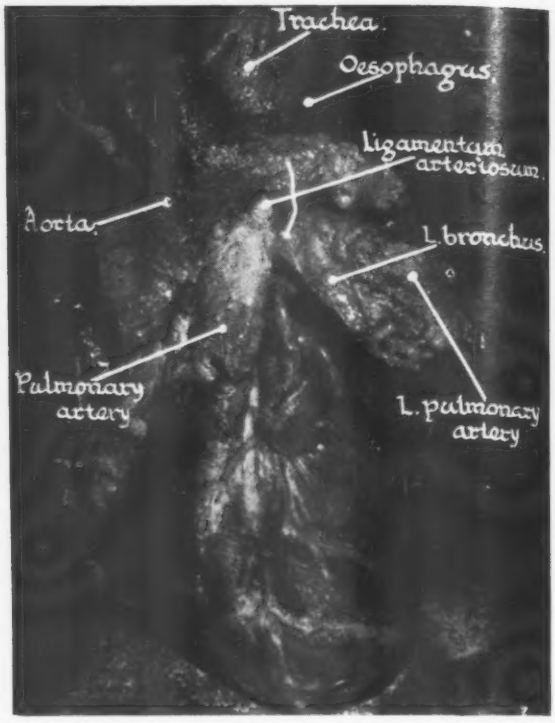

FIG. 3.—The same, left anterior oblique view. The left pulmonary artery has emerged from between the oesophagus and the trachea and occupies its normal position at the hilum of the left lung.

respiratory embarrassment was so great that immediate thoracotomy was considered imperative.

A left thoracotomy was performed. The lung was retracted downwards to expose an apparently normal aortic arch. The mediastinal pleura was incised above the aortic arch to permit the index finger to burrow through to the lower end of the trachea. A cord-like structure could be felt traversing the posterior wall of the trachea, but its identification was delayed until the aortic archway had been dissected out and the structures of the lung hilum exposed. The beginning of the left pulmonary artery was not located in its usual situation. Instead, the upper lobe arterial branches were followed upwards to find the parent vessel lying in the groove between the bronchus and the oesophagus. At this stage the anomaly became obvious. It is illustrated in the drawing (Fig. 1) and in the photographs of the dissected necropsy specimen (Figs. 2 and 3). The main pulmonary artery was unusually long and passed to the right of the trachea where the right pulmonary artery was given off. The left branch passed between the trachea and the oesophagus to gain the left hilum. It was firmly adherent to the trachea which was considerably constricted at this point. The remainder of the ring was made up of the ligamentum arteriosum, and pleural, neural and lymphatic tissue connecting the lung root to the pericardium.

Any attempt at correcting the fault was forestalled by the onset of cardiac arrest which, in spite of cardiac massage, proved irreversible.

Discussion

We do not intend setting out a detailed description of the vascular anomalies which cause stridor. The reader is referred to recent articles by Apley (1949), Gross and Neuhauser (1951) and Dolton and Jones (1952).

The history of the case described above is common to many of these abnormalities but there are some features which are worthy of comment. In the first place, the negative result of the investigations makes any remarks in this connexion speculative. Nevertheless, bearing in mind the appearance of the anomalous vessel at operation and necropsy, it seems probable that satisfactory films of the barium-outlined oesophagus would have shown an indentation in this region. Even more certainly radiographs of the trachea outlined with iodized oil would have shown narrowing. Opinion on the danger of this procedure varies. Most writers think it harmless, but Dolton and Jones (1952) and Smithells (1953) view it with disfavour because of the liability of these cases to respiratory infection.

A further method of investigation, angiocardiography, was not available.

The position in the respiratory cycle of the wheezing is of some interest. All accounts of vascular

anomalies, if they mention the phase in which stridor occurs, state that it is during inspiration. In the case we have described it was chiefly expiratory during the acute episodes and wholly so in the intervals between. This may be related to the change in arterial pressure during respiration.

Finally, a few remarks on the operation are indicated. Good pulmonary ventilation was maintained throughout, and it seems probable that death was attributable to sustained traction on the left lung, causing complete obliteration of the left pulmonary artery, and, by angulating the origin of the right pulmonary artery, reducing the circulation to the right lung.

Had death not occurred at that juncture, relief of the constriction might have been effected by division of the left pulmonary artery, either alone or with reanastomosis in front of the trachea, or with implantation of the distal end into the main pulmonary trunk, or by division of the ligamentum arteriosum with the object of allowing the main pulmonary artery to move to the right.

This case was under the care of Dr. J. H. Lawson and Mr. R. S. Barclay, to whom we are grateful for permission to publish.

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THE RESPONSE OF INFANTS TO A LARGE DOSE OF WATER

BY

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Whatever the mechanisms involved, the response of the adult kidney to a large dose of water has three characteristics: (1) a great increase in the flow of urine; (2) an extensive fall in its osmolar concentration; (3) the excretion of a volume of urine within a few hours and before the flow of urine subsides which is roughly equal to that of the water administered.

The ability of very young animals to regulate the amount of water in their bodies was first tested by Aschenheim (1919), Ohlmann (1920), Wengraf (1921) and Lasch (1923). The first two found that within three months of birth human infants did not excrete the whole of the test dose. This was not confirmed by Wengraf who found that the infants responded to the test dose by quickly raising the rate of urine flow and that extra-renal losses of water were large enough to account for the differences between the volume administered and that excreted by the kidney. Lasch (1923) then made a further study of the problem and concluded that in the first month of life infants only excreted an average of 55% of the test dose within four hours and that extra-renal losses were not enough to account for the remaining 45%. He further observed that the formation of urine returned to its initial rate within four hours, even if the whole of the test dose had not been excreted.

Adolph (1943) investigated puppies of various ages after giving them 5% of their body weights of water. The animals absorbed all the water but at 2 days of age they excreted less than half the dose within four hours, and the normal adult response was not acquired till the animals were eight to 21 days old. The method used to follow the excretion of water included a determination of losses by the lungs and skin. Adolph stated that the slow diuresis in young puppies continued for many hours but the chart published only covers the first four after the water had been administered. McCance and Wilkinson (1947) and Heller (1947, 1951) studied the response of the newborn rat to a test dose of water. This animal is less mature in many respects than the human infant at birth, and although the test dose was absorbed, this was not followed by any significant diuresis or fall in osmolar concentration of the urine. Little of it was excreted within the period of observation. The guinea-pig is more mature at birth than the rat, and Dicker and Heller (1951) found that the newborn of this species (see also Heller, 1951) responded to the test dose by a diuresis, but that the rate of flow never equalled that of the adult animals per unit of body weight and it subsided when little more than half the volume administered had been excreted by the kidneys. The authors did not make a special study of the extrarenal losses but their experience with the rat led them to conclude that these losses could not account for the difference (Heller, personal communication).

Barnett, Vesterdal, McNamara and Lauson (1952) took up some of these questions in premature infants, and found that, contrary to general opinion based upon animal experiments, the premature infant was fully as capable of lowering the osmotic pressure of its urine as an adult, although the minute volumes achieved during the diuresis were not equal to those of adults per unit of surface area. They attributed this to the low glomerular filtration rates in the premature infants. Ames (1953) established the importance of age in the human species by giving 3% of the body weight of water to groups of infants, some of whom were less than 24 hours old and others up to 3 months. The percentage of the dose excreted within three hours rose from 10% in the first 24 hours of life to about 55% at the end of the first week and 100% before the end of the first month.

The present investigations were undertaken some years ago (McCance and Naylor, 1952) to supplement the knowledge then in existence about the excretion of water by newborn animals. The adults and infants have been compared with respect to the three characteristics outlined above.

Subjects and Procedure

Ten normal babies (five boys and five girls) and seven healthy adults (six men and one woman) have been the main subjects for this investigation. The adults were tested after an overnight fast. They lay down on reaching the laboratory and only got up during the test to pass urine. They were not catheterized. After preliminary samples of urine and blood had been collected the subjects drank the test dose of water as quickly as possible and emptied their bladders at appropriate intervals over the next four hours. Additional samples of blood were sometimes taken. The dose of water administered was 5% of the weight of the body or approximately 6% of the weight of water in the body. Three other adults who were tested had to be rejected from the main series because they were unable to take all the water or subsequently vomited part of it. The results obtained on them have, however, been included in Fig. 3.

The 10 babies were aged 6 to 18 days. They were fed at 2 a.m. on the day of the test but not at 6 a.m. The test began between 8 and 10 a.m. A catheter was inserted and the bladder emptied. Urine was then collected for approximately one hour, and the test dose of water, again equivalent to 5% of the body weight, was administered by stomach tube. Thereafter the bladder was emptied at appropriate intervals for the next four hours. In five babies no samples of blood were taken and in five a sample was withdrawn after the diuresis had subsided. Only two of the babies were being breast fed. (Permission to make experiments has always been obtained from the mother of any infant investigated.)

Tests were made on five other babies, aged 6 to 39 days, who had been born with inoperable meningo-myelocoeles. These babies were given no food or water after midnight preceding the test. A catheter was inserted about 8 a.m. and the bladder emptied. A preliminary sample of blood was taken and urine collected for about an hour, then 15-20 ml. of a 10% solution of inulin was given subcutaneously, and after another hour a sample of blood was taken, the bladder again emptied and the test dose of water administered by stomach tube. Thereafter the bladder was emptied at intervals as for normal babies, and blood was taken at the height of the diuresis. This procedure proved unsuitable for part of the research in hand because the removal of the blood samples almost always interrupted the natural rise and fall of the flow of urine.

Vesterdal and Tudvad (1949) reported that painful injections caused a large fall in the inulin and para-amino hippurate clearances. They interpreted these results as being due to constriction of the vasa afferentia. In agreement with this Barnett and Vesterdal (1953) found that the fall in volume which followed painful stimuli was not accompanied by an increase in the concentration of urinary solids. Verney (1946), however, found that emotional upsets reduced the volume of urine in dogs by provoking a secretion of post-pituitary hormone and the results of Ames (1953) indicate that the same mechanism operates in human infants. Brod (1953) has reviewed the subject in an interesting and general way, and it is now certain that the responses to emotion may be very variable and may even lead to a diuresis (Miles and De Wardener, 1953).

Fig. 1 shows results obtained in one baby in the course of this investigation. The fall in volume was accompanied by a corresponding rise in the osmotic pressure of the urine. This indicates strongly that the response was due to an increased secretion of post-pituitary hormone and the time relationship of the fall to the stimulus is in agreement with this.

Chemical and Analytical Methods

All urines were stored under toluol. When blood was taken the sample was collected without anticoagulant and

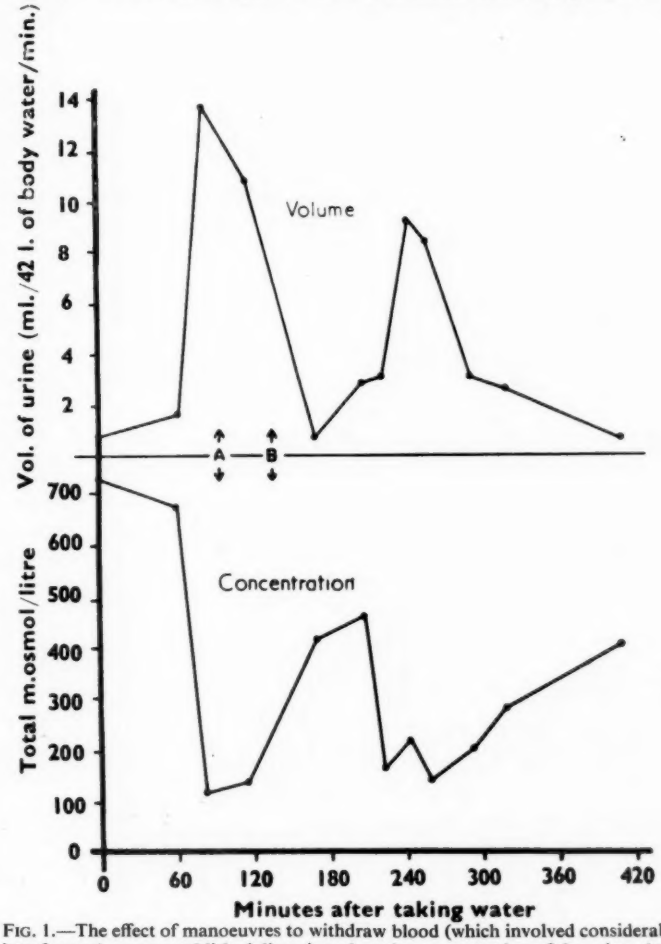

FIG. 1.—The effect of manoeuvres to withdraw blood (which involved considerable interference) on an established diuresis and on the concentration of the urine. At A no blood was obtained. At B blood was withdrawn from the femoral vein.

the serum separated as soon as possible. The osmotic pressures of all fluids were obtained from the depression of their freezing points (Hervey, to be published; Ramsay, 1949). The factor $\frac{1000}{1 \cdot 86}$ was used to convert these results to m.osmols./l. Urea in urine and serum was determined by Lee and Widdowson's (1937) method, creatinine by a slight modification of the method described by Hawk, Oser and Summerson (1947), sodium and potassium by the Beckmann flame photometer, and chlorides after Sendroy (1937). Inulin was determined by the method described for the estimation of fructose by Bacon and Bell (1948).

The body water of the babies has been calculated by assuming that an infant weighing 2·5 kg. contained 77% of water, one of 3·0 kg. 73% and one of 3·5 kg. 69% (Widdowson and Spray, 1951). The body of an adult weighing 70 kg. has been assumed to contain 60% of water, i.e., 42 litres (McCance and Widdowson, 1951). The 'average' curves shown in Figs. 2 and 4 were constructed by drawing the individual curves freehand through the experimental points and taking the values at appropriate times to average for the composite curves.

Results

Fig. 2 shows the average volumes of urine passed per 42 l. of body water per min. by the 10 babies and seven adults plotted against the time which had elapsed after the water had been given. This was taken as the mid-point of the period over which the dose was administered. Since Barnett *et al.* (1952) gave their results per 1·73 sq. m. per min. a curve has also been given in Fig. 2 for the volumes passed per 1·73 sq. m. On the basis of body water the infants excreted for a short time just as large a volume per min. as the adults and for a time did in fact excrete as large a percentage of the test dose per min. The rate of flow reached its peak in a little over an hour in the infants but not till about two hours in the adults. This difference is statistically significant but it is probably not of fundamental importance. It may have been due partly to the fact that it took slightly longer to administer the water to the adults than it did to the infants, but a more likely explanation seems to be that the dose, which was of a formidable size for adults, may have been help up longer in their stomachs (Jones, 1951). The size of the dose certainly influences the course of the diuresis, for Adolph (1943) has shown that the larger the dose the later the peak of the diuresis in adult man, and in work carried out previously (McCance, 1951), admittedly on other subjects, a much smaller dose was given and the peak of the flow came about 30 minutes earlier.

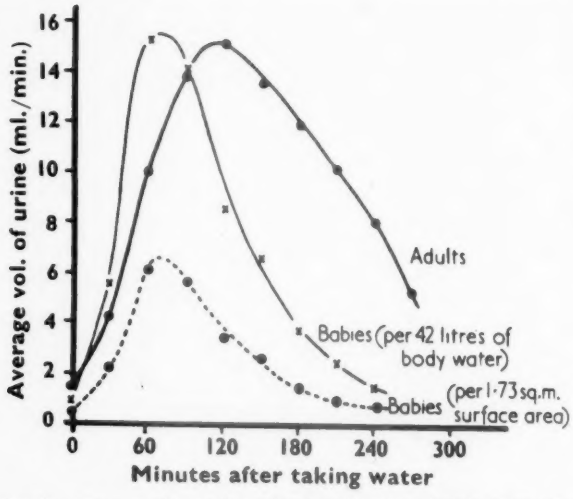

FIG. 2.—The rate of excretion of water after the administration of a dose equivalent to 6% of the weight of water in the body.

The rate of flow remained at a high level for a shorter time in the infants and had returned to its base line in four hours. The effect of this difference will be demonstrated later (Fig. 4).

Barnett *et al.* (1952) gave their premature babies aged 5-8 days 4% of their body weight of water, and in spite of this smaller dose obtained a diuretic response of about 7 ml./1·73 sq. m./min., which must have been about the same per 42 l. of body water as the one given by the present series. They gave their two adults only 2% of their body weight of water and obtained rates of urine flow of 12 to 13 ml./min. The average rate of flow obtained by McCance (1951) for adults after the administration of a dose equal to about 2% of the body water rose to 11 ml./min. The present results are in general agreement with those of Barnett *et al.* (1952) although the basis on which the infants were compared with the adults makes the volumes passed by Barnett's infants appear much smaller than they would have been had the comparison been made per unit of body water, and this has affected some of their conclusions and made them differ from those drawn in the present paper.

Table 1 shows the average volumes passed per minute by the adults and infants at the peak of the

TABLE 1
AVERAGE MINUTE VOLUME AND COMPOSITION OF THE URINE AT HEIGHT OF DIURESIS

	Adults	Infants
Volume ml./42 litres body water/min. ..	18·7	20·6
Urea (m.osmols/litre)	19·4	27·1
Cl (m.Eq./litre)	9·9	10·4
Na " "	11·9	11·6
K " "	6·5	6·5
Total osmolar concentration (m.osmols/litre)	70	81

flow of urine. This was not necessarily always the specimen of urine in which the osmolar concentration was at its lowest, and at comparable minute volumes the osmolar concentration was sometimes higher in the infants when the rate of flow was rising than it was when it was falling. Table 1 also shows the average concentrations of urea, Na, K and Cl and the total osmolarity. The urines were all very dilute and there was no significant difference between the infants and the adults. Some of the infants had higher concentrations of urea in their blood than the adults and this probably accounts for the slight difference in the concentration of urea in the urine. The infants, therefore, were able to dilute their urines as effectively as the adults. The work of Ames (1953) suggests that infants less than 48 hours of age would not have been able to do so. The present results are in entire agreement with those of Barnett *et al.* (1952) for infants of the ages studied by them and of Dicker and Heller (1951) for guinea-pigs but they differ from those of McCance and Wilkinson (1947) and of Heller (1951) for the newborn rat.

Fig. 3 shows the inulin or endogenous creatinine urine/plasma ratios of the infants from whom blood was obtained and of the adults plotted against the volume of urine passed per 42 l. of body water per min., both on logarithmic scales. Similar information has been given for newborn and adult guinea-pigs during a water diuresis by Dicker and Heller (1951) and for puppies during an osmotic diuresis by Dicker (1952). The present results show that at any given minute volume the urine/plasma ratios of these infants were very little lower than those of the adults, and that they were lower by the same proportion at all minute volumes. Since the creatinine or inulin urine/plasma ratio multiplied by the minute volume is a measure of the glomerular filtration rate, these results also show that at equivalent minute volumes the glomerular filtration rates of some of the infants were a little lower than those of the adults, although others had achieved the adult values. These infants were known to be of the age when the glomerular filtration rate per 42 litres of body water is of the same order as that of adults (McCance and Widdowson, 1952), and had younger or older infants been studied the probability is that their urine/plasma ratios and glomerular filtration rates would have been lower or higher at all minute volumes than those given by the present series. Be that as it may, the present results show that when the disturbance to the body water of adults and of infants of these ages had been the same, the urine/plasma ratios were similar and so were the glomerular filtration rates. They do not show that urine/plasma ratios and glomerular filtration rates as high as those of adults would have been obtained in dehydrated infants for this was not investigated (Calcagno and Rubin, 1950), but they demonstrate that when water was available for excretion, the diuresis was produced in the same way by infants and by adults. In other words the infants were not achieving a diuresis by increasing their glomerular filtration rates but by decreasing the amount of water reabsorbed.

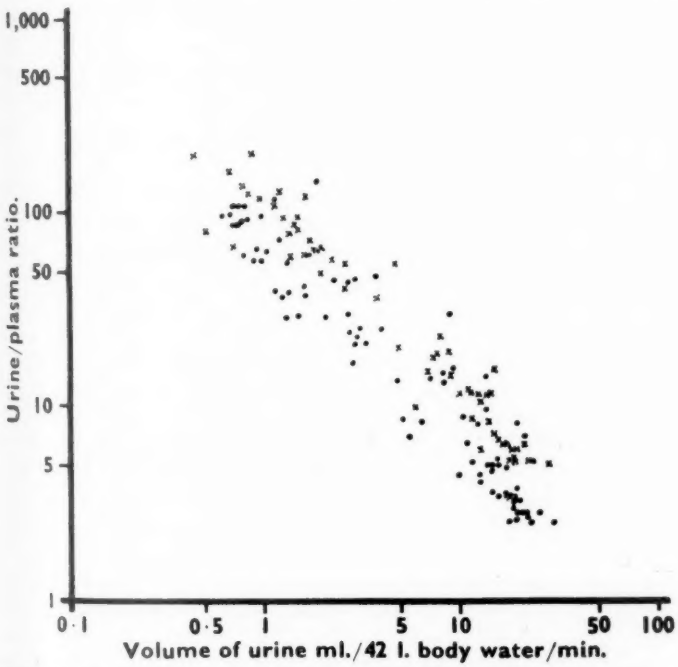

FIG. 3.—Variations of the urine/plasma ratio (inulin or endogenous creatinine) with the minute volume of the urine. × Adults. ● Babies. Both scales are logarithmic.

Fig. 4 shows the volume of the urine, expressed as a percentage of the water administered, passed by the end of each half-hour after the dose had been given. After one and a half hours the infants had excreted a larger percentage of the dose than the adults, and this is to be correlated with their rapid increase of urine volume shown in Fig. 2. After this time the adults continued to excrete large volumes of urine till at the end of four to four and a half hours a volume equal to that administered had been excreted. The infants' rate of excretion, however, rapidly declined (Fig. 2) with the result shown in Fig. 4. At the end of four hours the infants had only excreted a volume of

urine equal to about 57% of the volume of water which had been administered. This is in general agreement with the results of Ames (1953) for babies of this age. Barnett *et al.* (1952) did not investigate this matter for they terminated

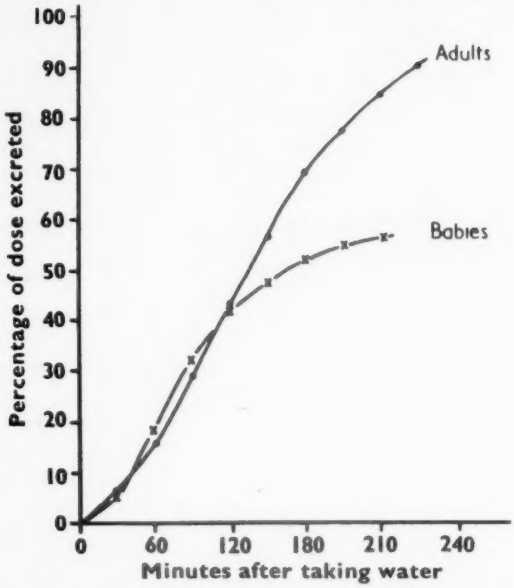

FIG. 4.—The percentage of the dose excreted after the administration of water equivalent to 6% of the weight of water in the body.

their experiments at the end of one and a half to two hours. The small volume excreted was not due to the magnitude of the extra-renal losses of water in infants, for this was measured in the same ward in 10 babies of similar age and weight and found to average 1·15 g./kg./hr.±0·57. This would only account for 9% of the volume of water given. Hence extra-renal losses in infancy will not explain the difference between the infantile and adult response even if no allowance is made for extra-renal losses by the adults. The incomplete excretion of the test dose may have been due to the infants not being well enough hydrated at the beginning (Falk and Benjamin, 1951) but this seems improbable (Ames, 1953). This failure to restore the *status quo* must be regarded as a real difference between the newborn and the adult. Lasch (1923) and Ames (1953) found it in infants, Dicker and Heller (1951) in guinea-pigs and Adolph (1943) in dogs. It has also been found in rats (McCance and Wilkinson, 1947; Heller, 1951). It is to be noted that a dose of water equal to 6% of the weight of water in the body (about 150 ml. for a 3 kg. baby) is not much greater than the volume of fluid administered in a baby's normal 4 oz. feed, and the response to water and food may be rather different from the response to water alone.

Discussion

The central matter for discussion is the extent to which infants differ from adults in their response to a large dose of water and the extent to which any conclusions about this may be influenced by the basis of comparison. The reasons for preferring a basis of body water to one of surface area have been set out by McCance and Widdowson (1952), and the present results, if they have involved minute volumes, have been compared with those of adults on the basis of body water. To show the difference, however, some of the results have also been given on the basis of surface area (see Fig. 2). At the stage of development reached by human infants at 6 to 18 days of age the administration by mouth of 6% of the weight of water in the body led to a great and rapid increase of urine flow. This flow subsided more quickly than it did in adults but on the basis of body water the minute volumes attained were the same. These infants could excrete as great a fraction of the administered water per minute as adults, and this conclusion is independent of any basis of comparison.

At the height of the diuresis the concentrations of Na, Cl and K in the infants' urines were as low as they were in the adults' urines. This would probably not have been true in the first two days of life (Ames, 1953) although foetal urine characteristically has a low osmolar concentration (McCance and Widdowson 1953). Under the conditions of hydration operating in these experiments the infants did not excrete within four hours a volume of urine equal to more than 60% of the water which had been administered, whereas adults excreted a volume equal to 95 or 100%. These conclusions are all independent of any basis of comparison.

At minute volumes which were equivalent on the basis of body water or of the dose of water administered, the infants had glomerular filtration rates very nearly equal to those of the adults, and they concentrated their glomerular filtrates to the same extent. Had the minute volumes of the infants been expressed per 1·73 sq. m. of surface area each urine would have appeared to have had a minute volume less than half as great as that shown in Fig. 3. The urine/plasma ratios would not have been altered, but each would then have looked as though it corresponded to a smaller minute volume, so that at any given minute volume the urine/plasma ratios of the infants would have appeared considerably lower than those of adults. It would have followed that the infants' glomerular filtration rates were lower and that the glomerular filtrates were being less concentrated at any given minute volume (McCance and Young, 1941). It might have been

inferred, particularly at low minute volumes, that these infants were unable to concentrate their urines to the same extent as adults. It is suggested that this would have been an unjustifiable conclusion, although it might have seemed the obvious one, and that this basis of comparison has been to some extent responsible for the view that an infant's kidney is in most respects functionally undeveloped and immature. There is no doubt that in some ways an infant's kidney is functionally immature and can be shown to be so, but the whole matter requires careful re-examination and particularly where the basis of comparison is likely to affect the conclusions. Barnett *et al.* (1952) found that the P/U ratio for creatinine in infants rose above the corresponding ratio in adults as the minute volumes rose to the peak of the diuresis. This may have been because their infants were given relatively much more water than their adults and so the infants' diuresis was nearer maximal than was that of the adults. There is no doubt that adults could have achieved much higher minute volumes than the work of Barnett *et al.* would indicate had they been given more water (see Table 1) and their urine/plasma ratios would have been correspondingly reduced.

The differences between the findings for human infants and for the newborn of other species have been outlined in presenting the results. It would appear that the human infant 6-18 days of age has a kidney which is much more mature than that of a baby or a rat 1 day old and rather more so than that of the puppy 2 days old. It seems to be comparable in development with that of the newborn guinea-pig.

It should perhaps be pointed out that the present results indicate only what the kidney does under the normal circumstances of its life. They give no indication of the diuretic responses which might be elicited after suitable pre-treatment with saline (Crawford, Schoen and Nicosia, 1952; Rosenbaum, Nelson, Strauss, Davis and Rossmeisl, 1953) or if food were to be given at the same time as the water.

The failure to excrete the whole of the test dose at the same rate as adults seems to be common to all the newborn animals so far investigated, and suggests that infants may be much more easily poisoned than adults by the continuous administration of water.

Summary

After a test dose of water equal to about 6% of the weight of water in the body, infants aged 6-18 days (1) rapidly increased their urine volumes till they were similar in magnitude to those of adults per unit of body water or per unit of water administered; (2) passed urines at the peak of the diuresis as dilute as those passed by adults; (3) did not (as adults did) excrete a volume of urine equal to that of the test dose within four to four and a half hours; (4) had glomerular filtration rates nearly equal to those of adults per unit of body water and treated the filtrate in the same way in its passage down the tubules. There was no evidence that a change in minute volume was brought about by a change in glomerular filtration rate.

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THE SERUM PROTEIN LEVELS OF NEWBORN AFRICAN INFANTS

BY

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It has been shown (Holmes, Stanier, Semambo and Jones, 1951) that the concentration of γ-globulin in the serum of apparently healthy adult Africans is considerably higher than that of Europeans. It is also known (Longsworth, Curtis and Pembroke, 1945) that, in white infants, the level of γ-globulin of the serum of umbilical cord blood is higher than that of the maternal blood taken on the day of delivery. The question arises whether the newborn African infant has as high a level of γ-globulin as the adult African, or whether it is born with the same level of γ-globulin as the white infant, and subsequently increases its γ-globulin to the African adult level. This question was particularly interesting because unpublished observations by one of us (M.D.T.) suggested that apparently healthy African infants aged 2-4 years, without active infections and without evidence of malnutrition, had γ-globulin levels nearly as high as those of adult Africans.

Certain mammals are known to absorb large amounts of γ-globulin from the colostrum and early milk. Thus, Hansen and Phillips (1947) showed that the serum of the calf at birth contained no protein with the mobility of γ-globulin, but such a protein rapidly appeared if the animal was fed colostrum within 24 hours of birth. Similarly, Mason, Dalling and Gordon (1930) measured antibodies of ewe's serum and colostrum and lamb's serum, and showed that the lamb obtained its antibody only by suckling. As it is now known that antibodies are modified γ-globulins (Tiselius and Kabat, 1939), this must have meant an increase in the lamb's γ-globulin level. It is highly improbable that such a process occurs in man, but it would be useful to exclude this possibility, which might be invoked to account for the high γ-globulin levels found even in young African children.

Another difference in the serum protein pattern of apparently normal adult Africans from the generally accepted normal figures is the lower level of serum albumin. This probably has a nutritional cause as the albumin levels increase and approach the European mean when the subjects are placed on a good diet (Holmes *et al.*). Longsworth *et al.* found in white subjects that whereas the mean albumin level of cord blood was close to that of normal adults, the albumin level of maternal blood was lower, a fact suggesting that the foetus has priority over the mother if the protein intake is limited. It would be of interest to find whether the low protein diet taken in this part of Uganda by all Africans, including pregnant women, is reflected in the albumin levels of the newborn.

Our first aim, therefore, was to repeat on African infants the observations made by Longsworth *et al.* on white infants. Later, we studied serum proteins in early neonatal life in order to exclude the possibility that infants may absorb globulins from colostrum and early milk.

Material and Methods

Blood from the umbilical cord was collected in clean, dry centrifuge tubes at the time of delivery from full-term infants born by normal delivery in the maternity wards of Mulago Hospital. The blood was allowed to clot, and centrifuged, and the serum was separated within 24 hours of the birth. The serum was stored in an ice box until analysed, which was not more than two days after the birth. A blood sample was taken from an arm vein of the mother on the day of delivery or the day after, and treated in the same way. For a later series of observations, blood was taken from the umbilical cord of infants delivered by caesarean section, and from the same infant, by fontanelle puncture, some days later, as late as possible before its discharge from hospital. In the interval, all the infants were breast fed and sucked well.

Serum proteins were measured by the Antweiler micro-electrophoresis apparatus, using barbiturate buffer *p*H 8·6, ionic strength 0·12, the dialysed serum being diluted 1 in 4 before analysis; total protein concentration and the percentages of each fraction could be obtained directly from the electrophoresis diagram.

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TABLE 1
ANALYSIS OF SAMPLES OF CORD AND MATERNAL BLOOD

	Cord Blood			Maternal Blood		
	Africans		Findings of U.S. Workers	Africans		Findings of U.S. Workers
Protein (*g./100 ml.*)	Mean	Range	Mean	Mean	Range	Mean
Total	5·31	4·80–6·48	6·18	5·61	4·44–7·06	7·17
Albumin	3·26	2·80–4·19	3·82	2·45	1·93–3·22	3·56
α-globulin	0·73	0·37–0·98	0·78	0·98	0·73–1·33	1·26
β-globulin	0·26	0·11–0·43	0·60	0·75	0·42–1·07	1·62
γ-globulin	1·03	0·66–1·52	0·97	1·42	0·89–1·97	0·72
Protein (*% of total*)						
Albumin	61·5	54·4–70·8	61·9	43·7	37·5–48·5	49·6
α-globulin	13·5	5·7–19·0	12·7	17·6	13·0–25·4	17·8
β-globulin	4·9	2·2– 8·2	9·7	13·5	7·3–17·6	22·6
γ-globulin	20·1	12·8–27·3	15·7	25·2	16·8–30·9	9·9

Results

In the first series, 14 samples of cord blood and 10 samples of maternal blood were analysed. (The sera from four of the mothers had to be rejected on account of haemolysis.) The results are shown in Table 1. In each case, the mean figures obtained by the American workers are shown for comparison. The first group of figures refer to absolute concentrations of the fractions in g./100 ml., the second to percentages of the total protein formed by each fraction. 'Alpha-globulin' is the sum of the α-1 and α-2 fractions.

The difference between the maternal and foetal albumin concentrations of the Africans is highly significant (t for the difference of means is 4·8, p= <0·001). The difference between the maternal and foetal γ-globulin level may also be considered significant (t=2·6, p=0·05-0·02). That is, African newborn infants have a significantly higher albumin level and lower γ-globulin level than their mothers. The difference in the β-globulin (lower in the infants) was too obvious to require recourse to the t test.

A comparison with the figures obtained by the American workers is of some interest. In the cord blood samples, the mean α-globulin is not significantly different nor is difference in mean γ-globulin significant (t for the difference of means is 0·66). Both the albumin and the β-globulin levels, however, are considerably lower in the African cord blood: for the difference in mean albumin levels, t=4·3 and p=0·001. (The difference in β-globulin levels was too great to necessitate using the t test.) In the case of maternal serum, all proteins except the γ-globulin show a significantly lower level in the Africans. The significance of the difference of mean α-globulin levels, which might be in doubt on inspection, was tested when t=3·2 and p=0·01-0·001. The mean γ-globulin level is about twice as high in African mothers as in white mothers, an obviously significant difference.

For the second series of observations, the results are shown in Table 2, together with the interval between taking the cord blood and the second sample. The two 3-month-old infants had been carefully looked after, and had received prophylactic anti-malarial treatment ('daraprim') since birth. Figures in brackets refer to percentages of the total protein, the others to concentration in g./100 ml. There is clearly no increase in γ-globulin during

TABLE 2
RESULTS OF SECOND SERIES OF OBSERVATIONS

	Cord Blood						Second Sample						Interval
Baby of	Total (g./100 ml.)	Albumin	Total Globulin	α	β	γ	Total	Albumin	Total Globulin	α	β	γ	
T.M.	4·82	2·95 (61·4)	1·87 (38·6)	0·31 (6·7)	0·25 (5·1)	1·29 (26·8)	4·25	3·14 (74)	1·11 (26)	0·40 (9·5)	0·12 (2·9)	0·58 (13·6)	12 days
N.N.	5·00	3·19 (63·9)	1·81 (36·1)	0·51 (10·2)	0·37 (7·4)	0·93 (18·5)	3·81	2·34 (61·7)	1·47 (38·3)	0·44 (11·7)	0·29 (7·6)	0·73 (19)	8 days
M.	4·32	2·96 (68·4)	1·36 (31·6)	0·40 (9·4)	0·14 (3·2)	0·82 (19)	4·40	3·08 (70·2)	1·32 (29·8)	0·49 (11·1)	0·23 (5·3)	0·59 (13·4)	9 days
J.O.	5·35	3·13 (58·5)	2·22 (41·5)	0·76 (14·3)	0·18 (3·4)	1·27 (23·8)	4·10	2·46 (60·2)	1·64 (39·8)	0·71 (17·3)	0·49 (12)	0·44 (10·4)	12 weeks
F.B.	4·87	3·32 (68·1)	1·55 (31·9)	0·65	0·14	0·76	—	3·90	—	1·25	—	0·34	12 weeks

the first few days or weeks of life. On the contrary, the level of this fraction fell in each case.

Discussion

The low level of serum albumin in the Africans' cord blood, and the even lower level in the mother's blood, are probably to be explained by the low level of dietary protein which is prevalent in Uganda. The extremely low level of β-globulin was an unexpected finding, particularly in view of the work of Symul (1950) who, using a chemical method of analysis, found all fractions in African cord blood close to the values obtained in European cord blood. However, our findings are in accord with those of van Oye and Charles (1951) who compared sera of African cord blood and African adults (using a chemical method) and found all fractions, but especially the β- and γ-globulin, lower in the cord blood.

The raised γ-globulin levels of apparently normal adult Africans and of white infants suggested the possibility that the γ-globulin level of the adult African represented a survival into adult life of an infantile trait, analogous to the survival, in the adult African, of certain anatomical features of infancy (Scott Brown, 1953). The above results exclude this possibility. Whereas the white infant is born with a γ-globulin level higher than its mother's, the African infant is born with a γ-globulin level lower than its mother's or than adult male Africans. The idea that a raised level of γ-globulin is an inherited racial trait is not absolutely excluded by these results, since inherited characters are not necessarily present at birth; the results, however, give the idea no support. It appears from the second series of estimations that, as with white infants (Poyner-Wall and Finch, 1950) there is a tendency for total protein and total globulin levels to fall during the first few weeks of life. There is clearly no sudden increase in γ-globulin as a result of suckling.

The question whether the greater percentage of γ-globulin in African as compared with European cord blood has any significance is a difficult one. It has been suggested (Mackey, 1953) that in a country such as Africa where many infections are hyperendemic, there would be, and has already been, selection in favour of the ability to produce antibodies readily. Thus, one might conjecture that if the supply of dietary protein is short, antibodies are made in preference to certain other serum protein fractions—say β-globulin. This interpretation is, however, highly speculative in view of the fact that so far there is not the slightest evidence that the extra γ-globulin of adult Africans is antibody globulin.

Summary

The serum protein fractions of African umbilical cord blood, maternal blood, and the blood of young African infants were measured by micro-electrophoresis.

The main differences, as compared with corresponding data on white persons, were significantly lower mean levels of albumin and β-globulin. In the maternal blood, mean levels of all protein fractions were lower in Africans, except for that of γ-globulin which was about twice as high. Thus, whereas in white persons the mean γ-globulin level of cord blood is slightly higher than that of maternal blood, in Africans it was significantly lower.

The mean α- and γ-globulin levels at birth were found to be the same as for white persons, and there was no increase in γ-globulin as a result of suckling.

The interpretation of these findings has been discussed.

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SOME DIFFERENTIAL CHARACTERISTICS OF CEREBRAL MOTOR DEFECTS IN INFANCY

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During the 13 years in which I have been studying the characteristics of physical activity of babies and young children with motor defects of cerebral origin I have again and again been confronted with diagnoses which describe presenting signs simply as 'pyramidal' or 'extrapyramidal'. With the greatest deference I would urge the importance of clinical analysis of available function in each affected child. Physical activity—the expression of interrelated activity of neural structures—appears as a single thing, a living mosaic showing cerebral function both mental and motor. Physical signs are signs of function; where the brain is incomplete they show function which by its abnormality reveals the absence of neural activity indispensable to normal function, that is, they show the presence of a lesion or lesions. A diagnosis of, for instance, 'pyramidal defect' is thus based on the location, by deduction, of inactive cells. Yet the defect is manifest through the behaviour of active cells of infinitely complex function—motor and mental. Hence, the terms pyramidal or extrapyramidal signs are not by themselves adequate to describe the nature of that remaining function upon which the child's potentialities and the planning of treatment depend.

The presentation of such elementary data is excusable on the grounds that little is known of the growth of function which lacks normal components, and it is only now becoming recognized that signs in the physical activity of a child with an incomplete brain show change as that brain matures. By comparison with the physical activity seen in normal children of the same age the clinician may assess the function, both mental and motor, remaining to a child with a non-progressive lesion of the brain and plan for its fullest exploitation. In this paper I am confining myself to a description of some of the less striking characteristics of physical activity in growing children with abnormalities of motor function from which, I believe, the nature of their residual *motor* function may be deduced. (I have described elsewhere (Collis, 1953) some characteristics of mental activity to be seen in the physical behaviour of infants.) The achievements of motor-deficient children rest not only on their mental capacity but also on the kind of physical handling they receive during the stages of 'plasticity' of the nervous system. For this reason it is important that their remaining equipment—mental, motor and special sense—should be assessed as early as possible in life and help provided for those of sufficient mental capacity.

Diagnosis of Motor Abnormality in Infancy

It is not yet universally accepted that diagnosis of motor defect in infancy is important. It is important because inappropriate handling of affected babies augments their motor abnormality, and handling which is based on the assumption that an affected baby is normal inevitably is inappropriate. It is not always accepted that differential diagnosis is important, yet it is important because treatment must be appropriate to the type of motor abnormality as well as to the child's mental status. Nor is it generally recognized that diagnosis of brain abnormality in infancy is possible where there are no gross signs. We find, however, that a history of defective breathing and sucking throughout infancy is commonly given in cases of motor abnormality and that most of these children are brought to the doctor in babyhood because the parents suspect that all is not well. This means that signs of neural abnormality are indeed present in babyhood though they are not the signs in the adult with neurological motor defect. Neurological signs must be specially looked for in infancy to prevent delay in instructing parents in the techniques of handling their motor-deficient babies.

For practical purposes, cerebral function in the infant may be deduced from observation of the infantile reflexes; these are fragments of the primary activity of the newborn baby and may be seen as he

is handled. The human brain is concerned, however, with thought as well as with movement, and in so-called voluntary movement, which includes speech, thought finds expression through the reflex motor apparatus. The change from infantile to mature activity happens in a gradual way and is most easily seen by observing modifications of the infantile reflexes which can be used as guides for assessing the normality or abnormality of developing mental activity.

Brain abnormality may affect mental processes and leave reflex motor activity intact. Modification of the infantile reflexes shows abnormality in such cases; in fact many workers have noted imperfect modification of infantile characteristics in mentally defective subjects; the grasping reflex, for instance, may persist in a relatively unmodified form up to a late age. At all ages mentally defective children show abnormality in their use of movement. On the other hand, brain abnormality may directly disorder reflex motor activity itself so that the infantile reflexes, the sucking reflex, for instance, are impaired and the abnormality is in movement itself and hence developing voluntary activity is distorted. Widespread abnormality of brain function affecting both the mental and motor aspects of physical activity is shown by a deficient use of movement which itself is abnormal. Though in the individual case movement itself, or its expressive use, or both parts of physical activity at once may be impaired by loss of brain cells, at examination the clinician is confronted with the two aspects simultaneously—physical activity. In order to diagnose abnormality and recognize normality in either aspect he must analyse this physical activity and distinguish between the two parts.

Alterations of Muscle Tone

That the normal young infant shows hypotonicity is well known, yet babies' limbs resist reflexly direct attempts to alter their flexed attitudes; both the hypotonicity and the resistance diminish as development proceeds. These and other changes express the evolution of intact brain activity; similarly, with the deficient brain, evolution of residual brain activity is expressed by changes in physical activity. Reflex motor activity is gradually modified during the stages of infant development and throughout life it serves to express thought, so even where this reflex function is defective motor signs change with mental development and movement is modified by thought. In mentally defective babies physical expression continues to be characteristically infantile; on the other hand, where developing mental activity can find only distorted expression because of motor insufficiency, there are characteristic signs of weakness and inadequate progress. Thus in cases of motor abnormality it is essential to distinguish modifications of movement which are related to mental activity from morbid signs. Though this distinction may not be easy, when signs are viewed as a whole and due weight is given to effects of any coexistent defect such as deafness, and if the malleability of nervous function in the young child is duly remembered, it is usually possible to estimate correctly available function, both motor and mental, in any given case.

While in children with the type of motor insufficiency characterized by ataxia there is no stiffness, in other types, though hypotonus remains as a sign, stiffening takes place as the child gets older. (Stiffness or opisthotonus in the very young baby occur among other signs of gross cerebral defect and present little diagnostic difficulty.) Where stiffening gradually develops as the infant gets older, this may be neuro-pathological in origin or may occur as force is exerted by or emotion aroused in the affected child. There are thus two possible sources of stiffening—the motor apparatus and the mental apparatus. In the child with an intact central nervous system stiffening of effort or emotion, even when widespread and associated with grimacing, is readily correctly interpreted by the observer, but in the motor-deficient child such stiffening may easily be mistaken for added dysfunction and, as such, attributed to the presence of a further lesion of the motor apparatus. Signs of mental activity, including this normal characteristic of stiffening, are not discernible in the very young baby and are absent or greatly diminished at physiological rest, for instance in sleep, in the older subject. When effects of mental activity—normal and abnormal—are subtracted from deficient physical activity, remaining characteristics indicate the nature of the motor function available to the child, and it is on these characteristics, which may or may not include stiffness, that differential diagnosis of the type of palsy should be based.

We have been able to distinguish only two types of stiffening of neuropathological origin in cases of infantile cerebral palsy; these we call spasticity and rigidity. Stiffness of either type varies in degree from case to case, but the reactions characterizing each type remain constant. While the type of stiffness we describe as rigidity may be present in the very young baby, the type we describe as spasticity develops relatively slowly. A difference in the early histories of children showing these abnormalities is usual. Rigidity is often a sequel of prolonged jaundice or of white asphyxia, while spasticity may develop in

a child who suffered birth trauma or in one who was normally born. Mental insufficiency (unless associated with specific physical abnormality such as microcephaly) cannot be diagnosed in the newborn child, but when gross signs of cerebral abnormality are present in early infancy the prognosis is poor; if a child has fits a guarded prognosis should always by given. In cases of rigidity a history of early signs is commonly given, and mental defect is, in our experience, invariable. In cases of spasticity and in cases where stiffness of non-pathological origin develops, a history of early signs may not be given; we think that in such cases less prominent signs have been missed. Usually, affected children show abnormal hypotonus and lack of normal advance throughout infancy, but in the absence of gross signs they are regarded as normal until they develop deformities.

Spasticity

The neuromotor abnormality we describe as infantile generalized spasticity can usually be differentiated from other types of motor defect before it attains its recognized clinical form and before the usual clinical tests for pyramidal defect are of value. Though spastic stiffness develops relatively slowly, two early signs indicate the presence of the neurological defect underlying its development. Where both these signs are present in a child up to 2 or 3 years of age the development of spasticity should be expected. First, with the child supine, the ankles are firmly grasped, the thighs rotated inward and sharply abducted (Fig. 1) resistance is abruptly encountered. Second, with the child prone, with his pelvis held in contact with the surface on which he is lying, one of his legs is passively flexed at the knee and the sole of that foot stroked firmly with the examiner's thumb nail (Figs. 4 and 5); the hip on the same side flexes. (Each reaction may be obtained repeatedly, and it should be noted that the second reaction differs from the well-known infantile 'withdrawal' which may persist in mentally deficient children whether or not motor dysfunction is also present.)

In infantile generalized spasticity postures of the limbs and body of the older infant show little change from those seen in the young baby; in most cases signs of mental defect are found. Though the young affected child is noticeably inactive and hypotonic, the Moro reflex is readily evoked; the sharp contrast between his slow and laboured voluntary activity and this hyperreflexia is often mistakenly regarded as evidence of abnormal 'nervousness' and fear. It is not fear; even the normal baby shows this sign at the time of birth before the emotion of fear can safely be attributed to him. Later on fear and 'the body jerk' may become related, but we cannot assume the presence of fear in the child with motor dysfunction who exhibits this hyperreflexia as a feature of his condition. Such a child cannot develop normal security of posture and is easily thrown off physical balance; it seems to me that physical insecurity, spastic stiffness, and inadequate modification of infantile reflexia sufficiently account for the supposed 'highly nervous' state of many affected children.

With the development of voluntary activity the deficient reflex motor apparatus produces that stiffening which indicates the nature of the abnormality; this spasticity is subject to modification and decreases as the child becomes more adept and speedy in the purposeful use of his limbs. In older children the gross clinical picture of Little's disease is seen only where there is severe mental defect, but in many children there is marked spasticity only in the legs; this develops during the period of evolution of use of the upper limbs when movements of the legs are still largely reflex. Voluntary activity of the baby's arms sets in train reflex leg movements; the baby drags his lower limbs when trying to crawl forward by using his forearms for support and so activates his abnormal reflex leg patterns; where these are subsequently reinforced by premature attempts to assist the development of walking, the impaired reflex apparatus has full play to establish grossly distorted lower limb activity. Such children require skilled assistance in all early achievements if the development of an abnormal gait is to be as far as possible averted.

As children with early signs develop, further signs characteristic of spasticity appear. The child's limbs resist stretching only when force is sharply applied to counter the postural tendency, and this resistance yields to sustained traction. Force meets no resistance where it assists the return of the limb to its habitual posture. Then, the two signs already noted in the infant become more marked, and with the older child lying in the supine position, when the ankles are firmly grasped, the thighs rotated inward and sharply abducted, the hips and knees flex abruptly and the lumbar curve increases as resistance occurs (Fig. 2). With the child in the prone position with the legs extended, the pelvis held firmly down and the hip adducted, when one leg is passively flexed at the knee, the hip on the same side flexes; at this stage no plantar stimulus is required to evoke the reaction. With the child placed and supported on his side with his legs extended in line with the trunk, when the uppermost leg is passively drawn backward and abducted, the under leg rises

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 6.

FIG. 6a.

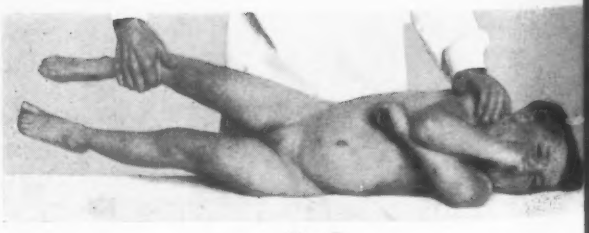

FIG. 7.

In Fig. 1, with the child (aged 3, spasticity not fully developed) supine, the ankles are grasped, the thighs rotated inward and sharply abducted, the hips and knees flex abruptly. Fig. 2 shows an older child (aged 5) in whom the sign is more marked. Fig. 3 shows the reaction of a normal child for comparison.

In Fig. 4, when with the child prone and the pelvis held in contact with the table, one of his knees is passively bent and the sole of that foot stroked firmly, the hip on the same side flexes. Fig. 5 shows a similar reaction of the other hip (same child as Figs. 1 and 6).

Fig. 6 shows same child as in Figs. 1, 4 and 5 pushed into a sitting position and Fig. 6a a normal child for comparison.

Fig. 7 shows same child as in Fig. 2 supported on his side with the legs extended in a line with the trunk; when the uppermost leg is passively drawn backward and abducted the under leg rises off the table.

Fig. 8 shows a normal child suspended by one ankle. This child is the twin sister of the child with spasticity shown in Figs. 8a-8d. Figs. 8a and 8b show retained extension of the freed leg on release of either ankle.

Fig. 8c shows the freed leg pushed into flexion. Fig. 8d shows the return of the freed leg to extension when pressure is released. Compare the postures of the head and arms with those of the normal twin child.

FIG. 8a.

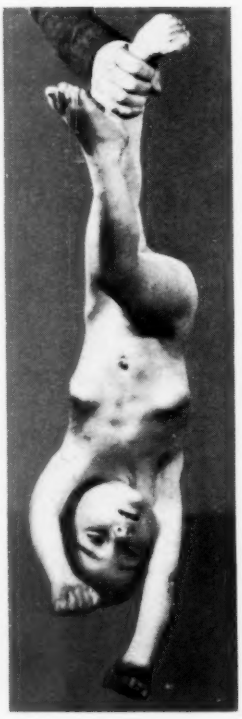

FIG. 8b.

FIG. 8c.

FIG. 8d.

FIG. 8.

off the surface on which it was placed (Fig. 7). With the child suspended by the ankles, the feet show inversion and plantar flexion (in contrast to the normal straight, strongly dorsiflexed feet), and on release of one ankle the freed leg may remain extended (Figs. 8a and 8b) or if the leg flexes the thigh rotates in; if the leg remains extended, when the examiner pushes it into flexion and then releases pressure from the sole of the foot, the leg spontaneously returns with characteristic precision to its former extended position (Figs. 8c and 8d). When the child is pushed from a supine into a sitting position with the examiner's hand behind his neck, his head may fall forward or 'poke', the back is rounded as in a young infant or is noticeably convex backward in the lumbar region; the legs show internal rotation at the thigh, flexion at the knee, plantar flexion at the ankle; the child's weight rests on the sacrum instead of on the tuber ischii (Fig. 6).

By the time these signs are present, whatever other abnormalities are found, a diagnosis of generalized spasticity could generally be made on better known pyramidal signs. The tendon jerks frequently show briskness. 'Spastic' briskness, moreover, is characteristic, the response being identical on repetitive stimulation, each response being of sharply limited range. This is usually particularly well seen at the knee joints. Clonus which is abnormally sustained may frequently be easily elicited at the ankle joints, especially with the child in the prone position with the knee kept passively flexed during application of the stimulus. The great toe may extend in a deliberate manner when the sole of the foot is firmly stroked. In addition to these well-known signs in these cases, with the child lying supported on his side with the legs extended, when the uppermost leg is passively drawn backward, abducted, and then released, it falls and remains with the hip flexed on the surface on which the child is lying. This sign is invariably present in hypotonic infants who later develop spasticity. In children with gross spasticity in whom this sign persists dislocation of the hips may be present or may supervene. Attitudes of affected children are determined by the character of their physical activity which includes the voluntary as well as the reflex aspect of movement. Abnormally sustained attitudes constitute deformity and this develops in most cases because voluntary movement is slowed and limited by the motor defect.

In the absence of hearing deficiency clear speech develops in intelligent children with spasticity; on the other hand, where there is mental defect, development of speech may be retarded and this abnormality is often mistaken for dysarthria, especially where other signs of retardation include imperfect mastication and dribbling; in such cases the palatal reflex is unimpaired, as it is in mentally abnormal children with spasticity whose speech is clear but 'chattering'. In contrast, in other types of motor disorder the palatal reflex is usually defective and there is dysarthria in addition to dribbling and imperfect mastication. Among signs of mental abnormality, squinting is common in children with spasticity, but this defect seldom persists throughout childhood and should be distinguished from persistent strabismus of other origins.

Rigidity

The other type of neuropathological stiffening we find where signs of spasticity are absent, and this we call rigidity. We have never found this condition apart from signs of mental defect which include incoherence of movement often so gross as to be termed by many 'athetotic movements'. A history of rhesus incompatibility or of asphyxia pallida is obtained in these cases; in some there is a history of prolonged jaundice in infancy. If a young baby is very stiff and shows opisthotonus and other signs of widespread cerebral defect, a diagnosis of motor abnormality is easily made in addition to that of mental defect. If, however, stiffening is slight and not constant and infantile hypotonus is prominent a diagnosis of motor deficiency may be more difficult in the early stages. Yet, in all cases of rigidity signs of both motor and mental abnormality develop as age advances, and when signs of mental activity are separated out from the physical activity of these children, neuropathological stiffness remains which differs from that of spasticity. In most affected infants the eyes tend to roll upward and the babies often appear to be blind because they do not focus; blindness is an uncommon complication, however. When these babies are brought into a sitting position the eyes no longer roll upward. To induce a sitting position in an infant who shows marked stiffness it is necessary to flex his head sharply, when the child's body flexes as it does in the Landau reflex. Many infants with pathological rigidity are found to be partly deaf, but deafness is often overlooked where the mental defect is gross. Abnormal responses to skin stimulation are often found.

In children with rigidity even where there is severe motor and mental defect, motor characteristics change somewhat with increasing age. Where stiffness was constant it becomes intermittent, while those babies who were only slightly stiff develop greater rigidity which also is intermittent. Thus, the clinical features which develop are identical in cases which show rigidity, though the degree of abnormality varies from child to child. The combination

of stiffness and gross incoherence of movement which develops in most affected children is the product of both motor and mental processes which are impaired in varying degree. When signs of mental activity are subtracted from physical activity the rigidity which remains is the diagnostic feature as far as motor abnormality is concerned. Children with rigidity of neuropathological origin showing intermittent stiffness are those whom we describe as having variable rigidity, and in these resistance to passive movement of a limb may abruptly cease and the limb become limp. In contrast to the resistance of spasticity that of rigidity is not altered by altering the speed of the passive movement. Stiffness and limpness of the child's limbs and body alternate abruptly. The alterations are not like those of 'cog-wheel' rigidity but are complete changes in the pliability of the limb and are usually associated with alterations of attitude of other parts of the body. Simultaneous changes of pliability are found in different limbs. This type of neuropathologically determined behaviour of the parts of the body seems to be unresponsive to the child's will; movements are usually stiffly performed with the limbs and body contorted, and incoherence of these movements may be very marked. Attitudes of head, limbs, and body, that is, postures characteristic of the mental and motor activity remaining to affected children, usually become abnormally sustained. For example, the arms may be rigidly extended with internal rotation at the shoulder, sometimes so extreme that the back of the elbow joint is turned toward the front of the body; the legs may similarly be rigidly extended and internally rotated at the hip joint. Even where these attitudes are so persistent as to constitute deformity and are even maintained during sleep, they may yield suddenly under the examiner's hands. In addition to these signs, the palatal reflex is abnormal. Rarely this is found to be hyperactive, in most cases it is almost inactive, dribbling of saliva is usually present, and swallowing, chewing and speech are deficient. Abnormality of respiratory movements is frequently marked throughout early childhood, and digestive troubles, including flatulence and vomiting, are common. Affected children are often ill nourished, and, as they grow older, deformity of the chest becomes marked in many cases. Sustained clonus, especially at the ankle joints, is often present, though the tendon jerks, when obtained, are normal, and, after infancy, the plantar response is equivocal or flexor. Tendon jerks and a clear plantar response are difficult to obtain in the presence of sustained rigidity.

Children with variable rigidity and incoherent movement must be distinguished from those in whom incoordination is of motor origin only and the stiffness which develops with age is the result of unimpaired mental processes activating impaired motor processes, and they must also be distinguished from children with spasticity. In children with variable rigidity the following abnormal reactions are found. When, with the child supine, the ankles are firmly grasped, the thighs rotated in and abducted, resistance may be encountered; in contrast to that of spasticity, such resistance is not augmented by increased speed of passive abduction, and instead of 'melting' under sustained traction it may abruptly yield at any phase of the passive movement or be sustained throughout. Attempts to flex the extended arm or leg may meet with similar resistance. Often there is no resistance to an attempt to extend the same limb immediately afterwards. When, with the child placed prone, with his pelvis held in contact with the surface on which he is lying, one of his legs is passively flexed at the knee and the sole of that foot firmly stroked, a withdrawal reaction takes place. This is characteristic of 'retardation' and occurs in a cumulative series of jerks as the stimulus is repeated; it thus differs from the reaction found in the presence of spasticity. With the child placed and supported on his side with his legs extended, the uppermost leg momentarily remains in abduction when lifted and released unless this manoeuvre is performed during a phase when resistance abruptly wanes. With the child suspended by the ankles, the feet show plantar flexion, and on release of one ankle the leg may remain stiffly extended, though the knee is not usually turned in as it is in the child with spasticity; when pushed into flexion the leg usually remains in the flexed position. When the child is pushed from a supine into a sitting position with the examiner's hand behind his neck, the trunk may fall forward with the head flexed and the back rounded. If this reaction is not immediate, passive flexion at the neck will usually produce it; the legs may be widely abducted and extended or may show flexion with the feet plantar flexed. In affected children mental development is slow and limited and symmetrical attitudes of the limbs only gradually succeed the tonic neck reflex attitude described by many authors for early infancy and for decerebrate rigidity. The physical characteristics of the older child, apart from the intractable fluctuating rigidity from which we have named this condition, depend largely on his mental capacity and hence are subject to modification by mental and emotional development.

Incoordination

Incoherence of mental origin in physical activity

differs from incoordination of motor origin. We have been able to distinguish only two types of motor incoordination in children with infantile cerebral palsy. These we call respectively ataxia and athetosis. Incoordination of either type varies in degree from case to case, but the reactions characterizing each type remain constant. While ataxia may be present in children with a history of gross signs of cerebral abnormality in early infancy, athetosis is found only in children with a history of asphyxia livida neonatorum who showed no gross early signs, or, rarely, in those with a history of early normality and subsequent asphyxia during a paroxysm of whooping-cough.

Infantile ataxia is, in our experience, a relatively rare type of palsy and the clinical picture which develops conforms rather closely with that seen in adult ataxia. When signs of mental activity are subtracted from physical activity the motor defect is that there is too little stiffening. The child with ataxia thus finds himself unable to move effectively against even the ordinary opposition of gravity. In the supine and prone positions he lies with widely abducted, externally rotated and extended limbs. with his feet in eversion and plantar flexion, and shows no resistance to passive displacement. With the child placed and supported on his side, the uppermost limbs fall when lifted and released. The leg falls into flexion if the hip is flexed before the limb is released and extension if it is extended. With the child held suspended by the ankles, the head fails to extend; the feet show eversion, and on release of one ankle the free leg falls into abnormally wide abduction. Well recognized signs, such as nystagmus or other eye defects, slurring speech, absent knee jerks, 'pendulum' reactions of the limbs, may also be found. In some cases hearing is defective. Where there were gross early signs mental defect is shown as development proceeds.

The unsteadiness of movement which underlies developing voluntary activity of children falling into the remaining group of infantile cerebral palsies is usually described as athetosis. However, the term athetosis (without fixed position) is often used to describe any incoherence or incoordination of movement irrespective of its origin, and this is confusing because there is no other diagnostic term to distinguish this last group from those in which signs already described are found. For lack of a diagnostic term for these cases, we have restricted to them our use of the term athetosis. In them, the sole abnormal characteristic of physical activity is generalized unsteadiness of movement including that of speech, and this abnormality must be distinguished from the incoherence of movement associated with mental defect and from the hyperreflexia already described, as well as from the ataxic type of incoordination. Partial deafness is occasionally found in children with athetosis. Though affected infants show abnormality of breathing, sucking and swallowing as a sequel of blue asphyxia, and though hypotonus is a sequel of their motor insufficiency, since gross signs are absent, early diagnosis is rare. Yet, in these cases early diagnosis is particularly desirable as even where the motor defect is of severe degree, normality of mental processes is found and hence under appropriate management the prognosis is favourable. With mental development, however, and especially where there is also deafness, the bizarre expression enforced upon mental activity by the motor disorder may mislead the observer. We are accustomed ordinarily to deduce people's mental and emotional processes from the expression of these in physical activity—in attitudes, in speech, in facial play, in gesture and in achievements. We assess mental growth in children by alteration in their physical expression and, normally, this includes not only increase in physical attainments but also decrease in physical insecurity and incoordination. Where, however, the motor activity underlying developing expression lacks the normal attribute of steadiness, affected children inevitably show insecurity and incoordination disproportionate to their mental growth. Hence, their physical instability may create a false impression of emotional instability or even of mental deficiency. Because ordinary achievements are too difficult for them such children grimace and stiffen with effort and when emotionally disturbed. These are normal reactions and it is normal to throw out the arms and plantar flex the feet when physically insecure, but in these children even these reactions are subject to distortion equally with other fragments of motor activity. Hence, when compared with normal easy movement, difficult movement and the effects of the difficulty may alike be taken for morbid signs and the results attributed to two coexistent motor lesions: a diagnosis of combined extrapyramidal and pyramidal abnormality is then given.

Stiffening of effort tends to 'fix' attitudes of insecurity and of effort, and, in time, these sustained attitudes constitute deformity. Further, as is well known, the tendon jerks may be affected by physiological stiffening, and incoordination may mask the nature of the plantar response; these irregularities may be mistaken for pyramidal signs. Since, however, the abnormal degree of stiffening exerted by these children is associated with effort it diminishes as effort is relaxed and tendon jerks are then found to be normal. Further, stiffening tends to mask

motor incoordination associated with mental activity. The motor state may be difficult to assess unless the complex interaction of motor abnormality and its results are separated. Reactions associated with mental processes are not found in early infancy, during sleep or at other times when mental activity is quiescent, in these phases 'athetosis' is not seen. When signs of mental activity are subtracted from the physical activity of affected children the diagnostic characteristic of motor incoordination remains. In contrast to the incoordination of ataxia where there is inadequate stiffening, the incoordination of athetosis results from inefficacious steadying mechanisms.

With the child in the supine and prone positions no abnormal resistance or lack of resistance is found when the legs are passively abducted, though the child may stiffen with effort. With the child placed and supported on his side, when the uppermost leg is lifted, the lowermost leg remains on the supporting surface beneath it; when released the uppermost leg momentarily remains abducted and usually shows marked unsteadiness and some stiffness of effort may be present. With the child suspended by the ankles, the feet show absence of the normal strong dorsiflexion and remain plantar flexed; on release of one ankle the leg may fall or may remain extended. When it falls the fall is wavering; if the extended leg is pushed down it stays down. Other signs of motor insufficiency in these cases include deficiency of the palatal reflex, inability to frown, raise the eyebrows, close the eyes normally or smile normally. Squinting is a normal phenomenon of early infancy, but it does not persist in children with athetosis, though the fists may be held closed, the infantile grasping reflex is not found, nor are other signs of mental retardation present.

Hemiplegia

Epilepsy, which is sometimes associated with combined mental and generalized motor defects, may also occur in cases of infantile hemiplegia. This last condition is usually easily distinguished from generalized motor defect; early flaccidity of one side of the body is sometimes noticed by vigilant parents. The signs which develop on one side are not dissimilar from those seen in generalized infantile spasticity; involuntary irregular movements of the disordered limbs may be seen in epileptic children with hemiplegia. In some cases the whole affected side is smaller than the other from early infancy; in other cases a discrepancy between the two sides of the body is not noticed until a later stage of development and seems to be accounted for by the relative inactivity of the palsied side in the absence of effective treatment. In the prone position with both knees flexed the child's body curves to the affected side. In our experience signs of mental abnormality are usually found in these children and their speech is usually retarded.

Conclusion

In conclusion, I have, perforce, recounted only some of the details of physical activity of motor-deficient children which, I think, help to differentiate their motor defects, and I have not described differing types of mental defect. Nor have I referred to likeness in details of physical activity. Yet, intact structures in incomplete brains have common function with similar structures in complete brains, and hence there are likenesses in physical activity to be described; these demand interpretation no less than do differences. I think that when both differences and likenesses are considered together reasonable explanations occur for some of the features of motor abnormality which are often regarded as puzzling. For instance, the apparent left-handedness of numbers of affected children, the relatively normal speech of most children with spasticity, the manner of development of characteristic deformity in each type of motor defect, the good use of the hands usually developed in children with spasticity and the poor use of the hands so commonly found in children with athetosis.

Summary

From observation of developing physical activity in babies and young children the clinician deduces the normality or abnormality of their maturing brains.

In physical activity, however, related motor and mental functions of the brain are simultaneously represented and each is of considerable complexity. Hence, deficiency in either must be separately assessed and remaining function analysed, for on the nature of this depend the planning and the outcome of appropriate management.

Deficiencies of cerebral motor function are discussed in this paper. An account of some of the simpler details of physical activity from which the type of defect may be deduced is given. Signs of mental defect are not described here.

Differences distinguishing the four types of abnormal motor activity covered by the general term the infantile cerebral palsies are described; two of these four types are characterized by abnormal stiffening and two by incoordination. The two types of stiffness and the two types of incoordination are

each separately described and differentiated. Likenesses in physical activity of affected children are not described. Relationship has been found between types and early histories.

Establishment of effective utilization of a deficient motor apparatus depends not only on the affected child's own efforts but also on the kind of help he receives in infancy. Thus rational physical handling can help all affected children apart from those in whom there is gross mental deficit. In a small proportion—perhaps 20% or even less—of all cerebral palsied children mental processes are entirely normal even where the motor disorder is extreme, and in these the prognosis is excellent if early appropriate help is given. For these especially should be made available the inestimable advantages of differential diagnosis and appropriate care during the stages of maximal plasticity of central nervous function.

I would like to thank Dr. David Lawson, the Physician Superintendent of Queen Mary's Hospital for Children, for permission to publish the photographs.

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DIFFERENTIAL DIAGNOSIS OF FACIAL AND DENTAL MANIFESTATIONS IN CONGENITAL SYPHILIS

BY

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A confident diagnosis of congenital syphilis can sometimes be made in children who appear otherwise normal from inspection of the facies and the mouth. Indeed, the observant doctor or dentist has in this way frequently been the means of discovering syphilis in a family. On the other hand, it is possible to mistake one or other of several conditions which in their facial and dental manifestations simulate congenital syphilis, and which, in view of the diminishing incidence of this disease, are likely to become relatively more common. This differential diagnosis is rarely referred to in textbooks on syphilology or paediatrics.

It is important that if there is syphilis in a family it should be discovered as early as possible so that those infected may have the benefit of treatment, and to prevent further members of the family becoming involved. But, for obvious reasons, it is equally important that congenital syphilis should not be wrongly diagnosed, and that it should be confidently rejected if it is not present. A high index of suspicion should be countered with great care so as not to make a diagnosis of syphilis negligently.

There are several conditions that mimic congenital syphilis in their manifestations in the face and mouth. The most confusing of these is the anhidrotic form of hereditary ectodermal dysplasia, which, the literature reveals, has frequently been misdiagnosed as congenital syphilis. In this condition the facies can be very misleading. The bridge of the nose is depressed so that it has a saddle-shaped appearance; the brow is high and wide; there may be scars on the face similar to the classical rhagades of congenital syphilis; and there are usually dental abnormalities, particularly of the permanent incisors and canines.

Many of the photographs of the faces of such cases in the published papers on the subject are almost indistinguishable from those seen in congenital syphilis, and the matter is further complicated by the fact that several members of a family may be affected. Careful observation, however, reveals several important differences. In hereditary ectodermal dysplasia there is no bossing of the frontal bones, but the depressed bridge of the nose may be exaggerated after puberty by prominent supra-orbital ridges. The 'pseudo-rhagades' radiate round the nostrils rather than the mouth, as is the case in congenital syphilis, and the lips tend to be thickened. The dental abnormalities are usually gross: there may be anodontia, or only a few teeth; there is gross disorder in the time of their eruption; many of the teeth, except the molars, are abnormally shaped, usually being small and conical, but they never show the morphological characteristics sometimes seen in congenital syphilis.

Diagnostic, however, in the fully developed syndrome is the absence of sweat glands—the most important component—the subjects thus being intolerant of heat. Also, in most cases, the head hair tends to be sparse and fine, and the eyebrows sparse; body hair may be deficient or absent. The nails may also show minor or gross defects.

Dental dysplasias, with little or no evidence of ectodermal involvement, may also cause confusion. However, careful examination of abnormally shaped teeth will reveal the differences between congenital syphilis and other dental dysplasias in which the typical Hutchinsonian tooth and its variants and Moon's (6-year-old) molars do not occur. Disordered timing of eruption and hypodontia are not features of congenital syphilis.

Reviews of the various types of hereditary ectodermal dysplasias include those by MacKee and Andrews (1924), Smith (1929), Cockayne (1933), and de Silva (1939). The dental abnormalities of congenital syphilis are well described in the illustrated paper by Cruickshank (1939).

The depressed bridge of the nose is a notorious stigma of congenital syphilis, but there are other conditions in which it occurs as well as the one already discussed. It is one of the features of gargoylism, but in this condition other signs, such

as mental defect and osteochondrodystrophy, usually make the diagnosis unequivocal; however, the enlarged liver and spleen and the cloudy cornea of gargoylism may raise doubts, although the nature of the corneal lesion is quite different from the interstitial keratitis of congenital syphilis. In the *formes frustes* of gargoylism some of the gross features may be absent, and differential diagnosis rendered more difficult if the bridge of the nose is depressed.

In achondroplasia the base of the skull is underdeveloped, and the normal development of the vertex causes the forehead to be relatively prominent, and so even exaggerate any depression of the bridge of the nose that may be present. However, other manifestations, particularly the diminished stature, usually make the diagnosis straightforward.

Depression of the bridge of the nose can be present without any other bodily abnormality. There is a considerable range of normal profiles in which the bridge of the nose is depressed, but there is a developmental anomaly which occurs by itself and which may lead to suspicion of congenital syphilis. This is partial or complete absence of the nasal bone (see Case 1).

In major conditions, such as the anhidrotic form of hereditary ectodermal dysplasia and gargoylism, clinical differentiation from congenital syphilis should seldom be difficult. It is in the minor conditions that confusion may occur, especially when other circumstances combine to aggravate the problem. The following two case histories illustrate the type of difficulty. They also illustrate the steps that sometimes require to be taken in order to eliminate congenital syphilis, bearing in mind that in this condition, especially in older children, serological tests are occasionally equivocal or even negative.

Case Histories

Case 1. A boy, aged 6, while under periodic observation for severe bilateral myopia developed cyclitis in the right eye associated with corneal oedema. Topical cortisone was started immediately and rapidly controlled the condition. The possibility of interstitial keratitis was considered, although the inflammation was arrested before there was time for the characteristic appearances to develop. A possible syphilitic aetiology was supported by the boy's facies. The blood Wassermann reaction was negative, but he was referred for an opinion.

Apart from the progressive myopia there was nothing significant in the previous history; there was no evidence of healed or active choroiditis. He had had recurrent "colds" for several years, but at no time was there any unusual nasal discharge.

He was of normal physical and mental development for his age. The facies is illustrated in Figs. 1 and 2. The most striking feature was the depressed, "saddle-shaped" type bridge of the nose; the forehead was prominent, but the supraorbital ridges were normal and there was no frontal bossing. The maxilla appeared to be slightly foreshortened, but there was no abnormality of the palate or dental arch. In spite of the nasal outline the facies did not give the general impression of being typical of congenital syphilis. The temporary dentition and the first permanent molars were all normal. Palpation revealed a deficient cartilaginous septum of the nose (Fig. 3). The nasal mucous membrane was normal, and there was no evidence of recent or past ulceration or destruction of tissues of the nose. No signs of syphilis were found elsewhere, nor was there clinical evidence of any other disease. Sweating function was normal.

FIGS. 1 and 2.—Facies showing depressed bridge of nose.

The routine blood Wassermann reaction was negative on two further occasions, and the cardiolipin Wassermann reaction, Kahn test, and Price's precipitation reaction were also negative. Radiographs of the wrists, elbows, and spine showed no abnormality. A radiograph of the skull showed that there was no nasal bone; the relatively horizontal angle of the unerupted upper incisors suggested some foreshortening of the maxilla, but no other abnormality was observed (Fig. 4). An intra-oral film showed that the unerupted upper central incisors were normal in shape.

FIG. 3.—Photograph illustrating deficient cartilagenous nasal septum.

The boy's mother and father both appeared to be healthy, and had normal facies. Neither was aware of any relative having a nasal deformity similar to that of their child. The mother had had a miscarriage before the

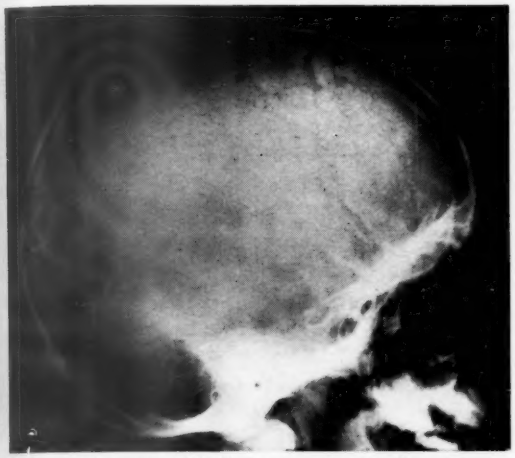

FIG. 4.—Radiograph of skull showing absence of nasal bone.

birth of the living child, and there had been no other pregnancies. The blood Wassermann reactions of the mother and father were negative.

It was decided that the child did not have syphilis. Topical cortisone was continued for several weeks, and there was no relapse of the inflammation on its withdrawal. No other treatment was given. The child has remained under periodic observation for a year, and there have been no further developments.

In this case the nasal deformity was ignored until the development of an inflammatory eye condition, when the combination of the two raised the necessity of considering a diagnosis of congenital syphilis. This condition was confidently ruled out, and the nasal deformity was found to be due to absence of the nasal bone. (Incidentally, this case illustrates the difficulty that may arise from the prompt use of topical cortisone in an inflammatory condition of the eye in children. The latter may never develop far enough to allow a clinical diagnosis, for example, syphilitic interstitial keratitis, to be confidently made. This disadvantage is, of course, outweighed by the beneficial local effect.)

Case 2. A boy, aged 14, was referred with a tentative diagnosis of congenital syphilis which had been made on the grounds of an abnormal dentition, supported by the results of serological tests on the boy and on his mother. He appeared to be healthy, and was well developed for his age (height, 5 ft. 7 in., weight, 140 lb.). The facies was normal, and there were no obvious stigmata of congenital syphilis. The dentition was grossly abnormal: a number of deciduous teeth were still present, some of the permanent teeth were missing, and some of those present were abnormal in shape (Figs. 5 and 6). The only two permanent upper incisors, however, were not Hutchinsonian, nor did they resemble any of the variants sometimes seen in congenital syphilis. Two of the lower incisors tended to be "screwdriver-shaped" and the lower canines were conical. The permanent molars were all normal, and one temporary molar was still present.

The hair on the scalp was rather sparse, and of fine texture; the eyebrows were sparse, and the pubic hair fine (Fig. 7). The nails and sweating function were normal. Clinical examination revealed no other abnormalities. Radiographs of the wrists and elbows showed no evidence of past or present disease of the bones. A radiograph of the jaws showed that some of the permanent teeth were unerupted and some were absent.

The boy had always been healthy, and there was nothing significant in the previous history, except that the first teeth did not appear until he was 3 years old. His mother appeared healthy, and showed no clinical evidence of disease. Her first husband died at the age of 27 from lobar pneumonia, and she had married again. There had been no children since her second marriage. There was one other child, a girl aged 15½, who was also healthy. The mother's and daughter's dentitions were normal.

The original report on the serological tests on both the boy and his mother stated that the Wassermann

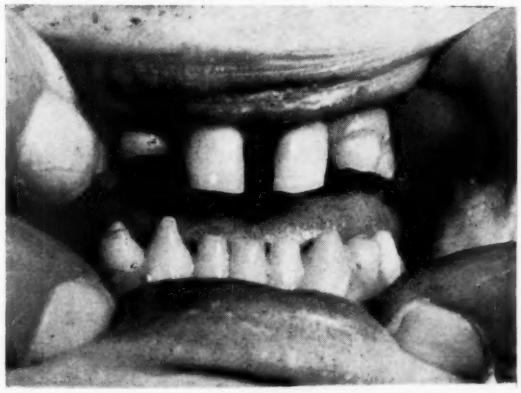

FIG. 5.

FIG. 6.

FIGS. 5 and 6.—Dental abnormalities.

The cast of the upper jaw was made at the age of 14, and the other photograph was taken two years later, but there had been no change in the dentition in the interval.

FIG. 7.—Photograph illustrating the sparse, fine pubic hair taken when the boy was 16 years old. There had been very little change in the appearance and distribution of the hair over the previous two years.

reaction was weakly positive and the Kahn test negative. These were repeated at two different laboratories and the Wassermann reaction and Kahn tests were reported negative in all instances. The sister's tests were also negative. The boy's Wassermann reaction and Kahn test were repeated four times during the subsequent six months, and on every occasion they were both reported negative. The report on the cerebrospinal fluid was: cells, 1 per c.mm.; protein, 20 mg. %; Wassermann reaction, negative; Lange curve, normal.

It was decided that the boy did not have syphilis, and no treatment was given. He has been observed at intervals over a period of five years. No further teeth have erupted, and a partial denture has been substituted for the unsightly upper front teeth. He is now practically bald, and the pubic hair is of approximately the same distribution and texture as when he was first seen at the age of 14. Otherwise he has developed normally.

Comment

In this case inspection of the teeth had prompted serological testing for syphilis. The results of these tests, and of similar tests on the boy's mother, were equivocal, but together were sufficient to arouse suspicion of syphilis. However, the dental abnormalities were not of the type associated with congenital syphilis, and no clinical evidence of this disease could be found. Repeated serological testing ruled out syphilis. The only other evidence of ectodermal defect was the slightly abnormal head and body hair. (Incidentally, this case illustrates the desirability of repeating serological tests for syphilis before drawing conclusions from them. The original results on both the boy and his mother were presumably errors attributable to some technical reason.)

Summary

Attention has been drawn to the significance of facial and dental abnormalities in the diagnosis of congenital syphilis. Confusion with syphilis may occur in such conditions as the anhidrotic form of hereditary ectodermal dysplasia; dental dysplasia, with or without other evidence of ectodermal defect; *formes frustes* of gargoylism and achondroplasia; and congenital maldevelopment or absence of the nasal bone. In view of the diminishing incidence of syphilis, these other diseases will become relatively more common.

Two illustrative case histories are reported in which congenital syphilis was suspected, but eventually ruled out. In one there was congenital absence of the nasal bone, and in the other, dental dysplasia. The cases also illustrate other aspects of the confusion that may occur under these circumstances, and the steps that have to be taken to eliminate congenital syphilis.

I am indebted to Mr. John Foster, F.R.C.S., for referring Case 1.

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HONEYCOMB LUNG AND XANTHOMATOSIS

BY

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In 1927 an unusual radiographic appearance of the lungs in which a peculiar meshwork was seen throughout both lung fields was described. The course of the associated illness was rapid, beginning with a paroxysmal cough and dyspnoea, and progressing to severe respiratory distress, cyanosis and death. At necropsy the radiographic appearance was seen to be due to a multitude of small alveolar cysts. There was some fibrosis and also what was described as an unusual type of granulation tissue with giant cells. To this condition the name of fibrocystic disease of the lungs was given (Kerley, 1927; Kerley, Shore and Young, 1927). In the following year a similar case was reported in which the condition was shown to be due to a generalized xanthomatosis (Rowland, 1928). Later, Berg and Vejlens (1939) and Berg and Zachrisson (1941) and de Fine Licht (1942) described the same condition associated with tuberous sclerosis.

Although the interest stimulated by this curious radiographic appearance is comparatively recent, the necropsy findings of a lung honeycombed with small cysts has long been recognized, especially in children. Sharkey described two children, aged 2 and 4 years, in 1894. Tooth (1897) recorded the condition in a baby of 18 months, Fletcher (1901) in a girl aged $3\frac{1}{2}$ and Bernstein (1905) and Hebb and Bernstein (1905) each in a girl aged 3 years. The morbid anatomy and histology of these cases is described in great detail, and comment is made upon the cellular infiltration of the cavity walls and the presence of giant-cells so characteristic of the cases to be described (Bernstein, 1905). It seems more than likely that, had radiography been available, a similar appearance would have been seen. Honeycomb lung (Fig. 1), the name given by Oswald and Parkinson (1949), is now a well recognized if rare radiographic finding and is easily distinguishable from other disseminated lung lesions such as miliary tuberculosis, pulmonary haemosiderosis and the pneumoconioses (Kerley, 1951). It is also distinguished from multiple lung cysts, usually confined to a part of a lung, by the uniformity of size and distribution of the component cysts.

This lung lesion has been reported in association with xanthomatosis, biliary cirrhosis, diabetes insipidus and tuberous sclerosis. A number of cases also have been recorded in which the cause has been obscure; in a few such cases a congenital anomaly has been postulated (Oswald, 1952). Children are not infrequently affected and of the 16 cases reviewed by Oswald and Parkinson (1949) seven were children. Three of these had xanthomatosis, two had biliary cirrhosis, while in the remaining two the diagnosis was obscure.

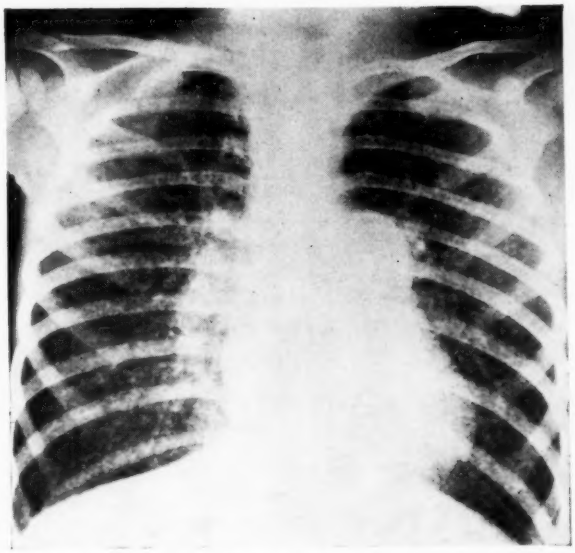

FIG. 1.—Radiograph of the chest showing diffuse honeycomb appearance and hilar enlargement in Case 3.

The purpose of this paper is to report three cases seen in the Royal Hospital for Sick Children, Glasgow, during the past five years, together with four further cases culled from the records of the hospital in which the diagnosis was made in retrospect on re-examination of the histological

material, the point of interest being that the underlying cause in each case was found to be generalized xanthomatosis.

Case Reports

Case 1. A girl aged 2 years and 9 months was admitted on January 15, 1948, with the diagnosis of Ollier's disease and miliary tuberculosis. She was an only child and her father had open tuberculosis. She had an uneventful early history apart from the chondrodystrophy which had been diagnosed at the age of 16 months. In October, 1947, she became fretful and listless, began to lose weight, and on April 26, 1947, she was admitted with a 'snow-storm' lung and tuberculous meningitis. This diagnosis was confirmed by culture and guinea-pig inoculation from the spinal fluid. She was treated with streptomycin and showed considerable improvement until March 5, 1948, when she suddenly deteriorated, becoming intensely dyspnoeic and cyanosed. She died on March 8, 1948. At necropsy there was seen in addition to the tuberculous meningitis and miliary tuberculosis, which were showing signs of resolution, a typical honeycomb lung with unequivocal histological evidence of a generalized xanthomatosis.

Case 2. A boy aged 19 months was admitted on September 20, 1948, with the complaint of increasing jaundice and dyspnoea. He was the youngest in a family of six; there was no relevant family history. His early history was unremarkable except for bronchopneumonia at the age of 5 weeks; this was followed by an attack of diarrhoea. In April, 1948 (at the age of 1 year), vomiting, anorexia and failure to gain weight developed; he soon became jaundiced and the urine was bile stained and his stools pale grey. Dyspnoea and a paroxysmal cough then appeared. The liver was palpable two fingerbreadths below the costal margin but there was otherwise no abnormality on clinical examination. A radiograph of the chest showed the characteristic appearance of honeycomb lung and of the skull that of Hand-Schüller-Christian disease. His condition deteriorated rapidly and he died on August 19, 1948. At necropsy he was found to have a diffuse xanthomatosis with multiple, thin-walled cysts of the lung. The liver also was xanthomatous.

Case 3. A girl, aged 2 years and 10 months, was admitted on February 2, 1952, with the complaint of a spasmodic cough and pyrexia, and dyspnoea with occasional cyanosis. She was the youngest of four; there was no relevant family history. Her early history was unremarkable except that she was rather slow to thrive. In February, 1952, she developed a spasmodic cough which became very severe and was later accompanied by cyanosis.

On admission she was a thin, wasted child with sordes on the lips. Her respirations were rapid and rather distressed but there was no clinical abnormality detected in the chest. The liver was palpable four fingerbreadths below the costal margin. A radiograph of the chest showed a well marked honeycomb appearance (Fig. 1). Her condition deteriorated rapidly and she died on March 1, 1952. At necropsy there was a generalized xanthomatosis with multiple, thin-walled cysts of the lungs and xanthomatous involvement of the liver.

The records of four similar cases in which 'multiple alveolar cysts' had been found post mortem were examined.

Case 4. A girl aged 2 years and 2 months was admitted on November 13, 1920, with a complaint of severe dyspnoea, cough and cyanosis. She was the sixth child in a family of seven; there was no relevant family history. Her early history was uneventful and she was well until November 4, 1920, when she developed a cough and dyspnoea. On admission she was slightly cyanosed and showed marked respiratory distress. Abundant fine râles were heard in the chest; the x-ray appearance was described as a 'discrete mottling' and ascribed to miliary tuberculosis. The child died on November 20, 1920, and at necropsy there was a conspicuously honeycombed lung which on re-examination of the histological material was seen to be xanthomatous.

Case 5. A boy aged 3 years and 2 months was first admitted on May 28, 1926, with a complaint of cough and dyspnoea. The younger of a family of two, he was healthy at birth and throve and developed normally. There was no relevant family history. Apart from measles he had no previous illnesses and was well until April 4, 1926, when he developed a cough, respiratory distress and fever. Bronchopneumonia was diagnosed. On admission he was found to have a liver enlarged two and a half fingerbreadths below the costal margin; abundant fine râles were heard over both lungs. The x-ray appearance of the lungs was described as a 'snow-storm lung' and diagnosed as miliary tuberculosis. He remained reasonably well and was dismissed home. Thereafter his condition remained unchanged until in March, 1927, when he became intensely dyspnoeic and cyanosed. He was re-admitted and died on March 28, 1927. At necropsy there was a honeycomb lung associated with generalized xanthomatosis with fibrosis of the liver and pancreas.

Case 6. A girl aged 17 months was admitted on November 26, 1930, with the complaint of abdominal swelling and progressive dyspnoea. She was the younger of two and there was no relevant family history. She throve and developed normally and was well until two months before admission when she became listless and increasingly dyspnoeic. Her parents also noticed an increasing abdominal swelling. On admission she was found to have enlargement of both liver and spleen but no signs referable to the lungs. She died on December 17, 1930, and at necropsy was found to have a honeycomb lung associated with enlargement of both liver and spleen. Re-examination of the histological material available demonstrated a generalized xanthomatosis with early portal cirrhosis of the liver.

Case 7. A boy aged 1 year was admitted on June 7, 1934, with a history of spasmodic cough and loss of weight. He was an only child and there was no relevant family history. He was healthy at birth but was slow to thrive and after the first few weeks of life had bouts of

coughing. Following an illness described as pneumonia at the age of 5 months, his cough became more severe and spasmodic. On admission a radiograph of the chest was reported as showing multiple cavities, and congenital bronchiolectasis was diagnosed. He was re-admitted on December 22, 1934, with intense dyspnoea, fever and cyanosis, and died on January 7, 1935. At necropsy multiple lung cysts were found and re-examination of the histological material showed a secondarily infected honeycomb lung.

Pathology

With minor exceptions the pathological findings in these cases have been so similar that a general description will serve.

To the naked eye the lungs appeared voluminous and mottled, with paler and more solid areas alternating with translucent cystic areas under the smooth pleura. On section the uniform size and distribution of the cysts gave the characteristic honeycomb appearance (Fig. 2). The diameter of these cysts varied around a mean of 0·25 cm.

Histology. The histological picture was as consistent as the naked-eye appearance. The cysts appeared to be distensions of alveoli, atria and respiratory bronchioles. Involvement of larger bronchioles, as indicated by the presence of muscle in the cyst walls, could not be detected. Septa and alveolar walls were irregularly infiltrated with histiocytes. These histiocytes were densely packed polygonal cells with oval or indented nuclei and cytoplasm often filled with lipoid material. These lipoid-containing histiocytes constitute the xanthoma cell characteristic of Hand-Schüller-Christian disease and allied disorders. Aggregations of this xanthomatous tissue were also seen forming discrete tubercles. These were easily distinguishable from those of tuberculosis by the absence of an endothelial reaction and necrosis, but the presence of giant cells, although scanty, and of eosinophils, might suggest a diagnosis of Hodgkin's disease (Fig. 3). Where tissue preserved in formalin was still available, frozen sections were stained with a mixture of Sudan III and IV. Lipoid was found in every case but could not be related in amount to the intensity of the histiocytic reaction. In some instances the cysts were lined with lipoid-filled giant-cells (Fig. 4). Weigert's stain demonstrated the destruction of the elastica in the alveolar and atrial walls where histiocytic infiltration had occurred. The mechanism of cyst production seems to be a combination of this destruction of elastic tissue and obstruction of the respiratory bronchiole by aggregations of xanthomatous tissue.

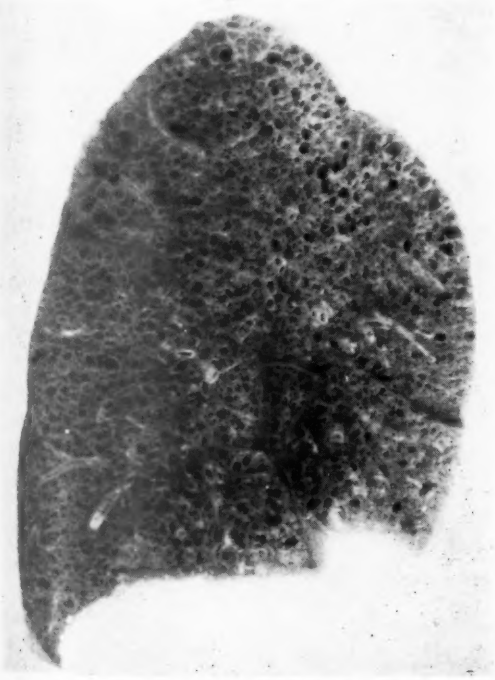

FIG. 2.—A vertical section of the right lung of the same case as in Fig. 1. The general cystic condition of the lung is shown.

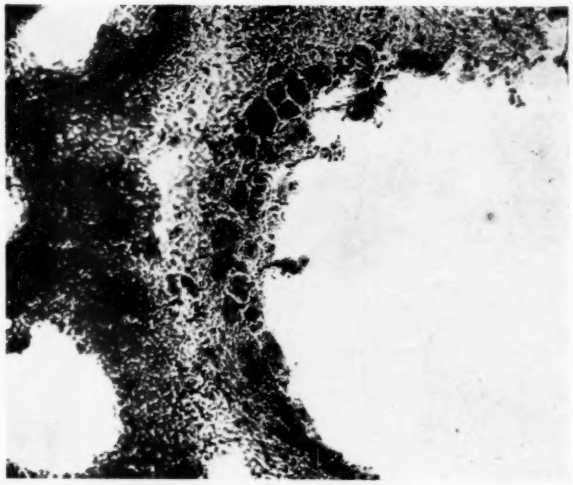

FIG. 3.—Photomicrograph of a cyst showing fat-laden giant cells in the wall. Xanthomatous tissue is present adjacent to this cyst with intracellular fat appearing dark. Sudan III and IV × 45.

In only five cases was liver tissue available for examination, and in four of these, xanthomatous infiltration of the portal tracts with obstruction of the bile ducts was found. In some sections merely a portal cirrhosis could be seen, not in itself diagnostic of xanthomatosis. Lipoid could be demonstrated in the macrophages lining the large ducts and in the Küpfer cells. Pancreatic fibrosis was noted in one

case while in the lymph nodes the loss of follicular definition together with the presence of giant-cells

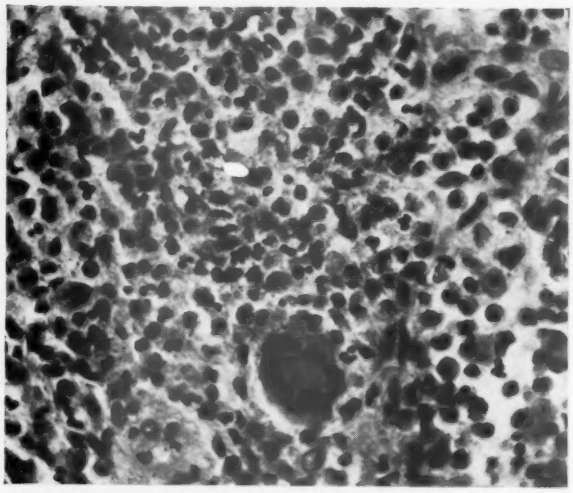

FIG. 4.—A xanthomatous mass to indicate the variety of cells which may be found in such tissue. There is a giant-cell surrounded by histiocytes, round cells and eosinophils. Haematoxylin and eosin × 150.

and eosinophils was suggestive of Hodgkin's disease. In the spleen there was an ill-defined histiocytic infiltration with scanty giant-like cells and eosinophils.

Discussion

The clinical picture of paroxysmal cough and dyspnoea in combination with the radiographic appearance of honeycomb lung is so striking and so immediately recognizable as to arouse one's interest in its pathogenesis in spite of its undoubted rarity.

Clinically there is a strong resemblance to idiopathic pulmonary haemosiderosis as described by Wyllie, Sheldon, Bodian and Barlow (1948) and this, indeed, was our initial diagnosis in the second case. Pulmonary haemosiderosis, however, is associated with attacks of haemolysis which a haematological investigation will serve to demonstrate and, moreover, does not show the honeycombing characteristic of pulmonary xanthomatosis (Gellis, Reinhold and Green, 1953).

The diagnosis of xanthomatosis in our cases may perhaps require some elaboration. The classification of the reticulo-endothelioses has recently received considerable attention, and there is now some evidence for regarding Hand-Schüller-Christian disease, eosinophilic granuloma of bone and Letterer-Siwe disease as merely variants of the same disease (Wallgren, 1940; Farber, 1941; Jaffe and Lichtenstein, 1944); intermediate forms occur comprising a complete range of reticuloses between Hand-Schüller-Christian disease on the one hand and Letterer-Siwe disease on the other. In all these conditions a consistent cytological picture prevails, namely an infiltration of histiocytes with scanty giant-cells and a variable number of eosinophils. The term xanthomatosis implying, as it does, the presence of lipoid, would seem to be inadequate for such a range of disorders. There are, however, cogent arguments against this view of the unity of all reticuloses (Siwe, 1949). It is to be expected that there would be a similarity between different disorders of the same system and this in itself cannot be held to justify the assumption that they have a common pathogenesis.

As far as our series is concerned lipoid was demonstrable in every case. The amount of stainable fat, however, bore no relation to the intensity of the histiocytic reaction nor was it to be found in every aggregation of histiocytes. Thus in certain areas the histological picture might resemble a non-lipoid reticulosis, the lipoid only being demonstrable on more searching examination.

In restricting the concept of xanthomatosis for the purposes of this communication to that of a lipoid reticulosis, we are supported by the fact that in all the cases of honeycomb lung cited, in which there was an associated xanthomatosis, it was a lipoid reticulosis that was described. It seems likely, moreover, that Letterer-Siwe disease would be too acute and eosinophilic granuloma of bone too localized to be responsible for such a lung lesion.

Nevertheless, in view of the variable histological picture encountered in this condition it seems possible that some errors in diagnosis have occurred. We have already indicated that the presence of giant-cells and eosinophils may simulate Hodgkin's disease and that special fat staining may be necessary for correct diagnosis. In the case of honeycomb lung reported by Douglas and Claireaux (1953) it would be instructive to know whether a lipoid reticulosis had been excluded by this means.

In most of the recorded cases of honeycomb lung in childhood the pathogenesis has been ascribed to xanthomatosis, biliary cirrhosis or tuberous sclerosis. In addition a few cases of obscure origin have been recorded in which there was no evidence of any of these conditions. Berg and Zachrisson (1941) record one and Oswald and Parkinson (1949) record two such cases: each had in addition, symptoms of diabetes insipidus. From the foregoing it seems likely that there is some link between these and a generalized xanthomatosis and that some recorded cases of obscure origin also have this basis. It is

tempting to suppose that the cases of biliary cirrhosis in which a honeycomb lung was found were similar to our own cases and that they, too, were xanthomatous. However that may be, in each of our seven cases, representing the sole yield of more than 30 years' necropsies in an active teaching hospital, the diagnosis has been shown to be xanthomatosis. It seems justifiable, therefore, to suggest that in childhood at least the clinico-radiographic picture of paroxysmal dyspnoea and honeycomb lung should be regarded as most likely due to a generalized xanthomatosis. Tuberous sclerosis, the other possible cause, is an even rarer condition than pulmonary xanthomatosis and can be recognized from the stigmata of the disease.

Although biopsy of a lymph node will in many cases provide the diagnosis, the clinical course of xanthomatosis is such that death will not be long delayed and post-mortem examination will reveal the nature of the disease.

Summary

Seven cases of honeycomb lung are described in which the causative condition was found to be a generalized xanthomatosis. It is suggested that in childhood xanthomatosis is the likeliest cause of this clinical and radiographic picture.

We are grateful to Professor Stanley Graham and Dr. J. H. Hutchison, O.B.E., for permission to report these cases.

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FEMALE PSEUDOHERMAPHRODITISM WITH ADRENOCORTICAL FAILURE IN IDENTICAL TWINS

BY

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The adrenogenital syndrome of prenatal onset has been described many times, and its association with adrenocortical failure is well known.

Wilkins in 1948 collected 99 cases, of which 16 were male and 83 female. Ten of the male and six of the female cases had associated adrenocortical failure. Since then 35 further cases of this association of syndromes have been reported; 12 were male and 23 female (Allibone, Baar and Cant, 1947; Tepper, 1949; Zuelzer and Blum, 1949; Panos, 1950; Hinman, 1951; Knudson, 1951; Jailer, 1951; Crigler, Silverman and Wilkins, 1952; Doxiadis, 1952).

The condition is known to occur in siblings, but has not previously been described in identical twins.

Of the 51 children with the adrenogenital syndrome and associated adrenocortical failure, only 16 had survived beyond the age of 12 months at the time of reporting. The others died in infancy as a result of adrenocortical failure. Of the 16 children who survived for more than one year, four died at 20 months, $3\frac{1}{2}$ years, 6 years and 4 years respectively. The others were kept alive by constant medication with salt, D.O.C.A., and, latterly, cortisone, in various combinations. Only one case has been reported in which it was possible to withdraw salt and D.O.C.A. at the age of 14 months without adverse effects (Doxiadis, 1951). The oldest of the survivors was 11 years at the time of reporting (Gardner, Sniffen and Zygmuntowicz, 1950; Butler, Ross and Talbot, 1939).

The twins described here are therefore of interest both as medical curiosities, and as illustrating the problems involved in the management of this condition.

Case Reports

The babies were born in the Whittington Hospital on July 29, 1952, after an uneventful 37-week pregnancy. The delivery was normal.

Both parents are well, there are three healthy siblings, and there is no family history of genital abnormalities or deaths in the neonatal period.

The first twin, Raphael, weighed 6 lb. 8 oz. at birth, and the second, Evelyn, 7 lb. 4 oz.

The genital abnormalities were noticed at birth, and consisted of enlargement of the labia majora which were covered with rugose skin, and hypertrophy of the clitoris, which resembled a hypospadic penis. No testicles were felt.

The babies looked alike (Fig. 1), both had a cutis navel, and the placenta and sac were single. Subsequent examination of the blood at the Blood Group Reference Laboratory, the Lister Institute, provided strong supportive evidence for their being identical twins (Table 1).

On the second day of life they were examined by Mr. Innes Williams of The Hospital for Sick Children, Great Ormond Street, who demonstrated a urogenital sinus into which opened the urethra and a vagina of considerable capacity.

In view of this last finding it was felt that the genital abnormality was most probably one of female pseudohermaphroditism due to congenital adrenal hyperplasia, and therefore it was easy to interpret correctly the signs and symptoms of adrenocortical failure when they appeared.

On the fourth day of life Evelyn vomited once but was otherwise well, while Raphael vomited repeatedly, refused feeds and looked pale and dusky. She was therefore given 1 g. of extra salt on that day in the form of normal saline by mouth, and in addition, vomited feeds were replaced with normal saline. However, she continued to vomit.

On the sixth day Raphael weighed 5 lb. 13 oz. and was

TABLE 1

BLOOD TYPING RESULTS

	A.B.O.	Phenotype	Probable Rh	M.N.	S	P	Lu	Le^a	Le^b	Fy^a
Raphael McC. ..	0	CcD^uEe	CD^ud/cdE	M	+	+	−	−	+	+
Evelyn McC.	0	CcD^uEe	CD^ue/cdE	M	+	++	−	−	+	+

FIG. 1.—The twins at 3 months.

noticed to have frequent, momentary attacks of pallor and cyanosis, accompanied by pursing of the lips and spasm of the eyelids. Respirations were deep and rapid. Intramuscular D.O.C.A. was therefore also given (2 mg. on the sixth day). Although there was no evidence of infection, a brief prophylactic course of chloromycetin was started. On the seventh day vomiting was less frequent.

The baby's serum electrolytes were as follows:

Serum chlorides . .	. .	531 mg. per 100 ml.
Serum potassium	. .	29 mg. per 100 ml.
Urinary chlorides	. .	345 mg. per 100 ml.

On this (the seventh) day Evelyn vomited again and had lost 3 oz. in weight, and her serum chloride level was 522 mg. per 100 ml.

Thereafter both infants were given increasing amounts of salt by mouth, and D.O.C.A. intramuscularly, the dosage being guided by the incidence of vomiting, the eagerness to feed, the state of hydration and the general appearance of the babies (Fig. 2).

On the eighth day Raphael was definitely dehydrated and required subcutaneous fluids which were given as normal saline. Vomiting persisted, however, and on the following day became projectile. She continued to have attacks of pallor and facial spasm, and the temperature rose to 102°.

The dosage of D.O.C.A. was increased with little hesitation since it is known that these babies can tolerate large amounts with impunity (Panos, 1950). The largest doses were given to the twins on their ninth day of life, when Raphael received 9 mg. D.O.C.A. as well as 2 ml. eucortone and $\frac{2}{3}$ g. salt (partly as subcutaneous normal saline) and Evelyn received 4 mg. D.O.C.A. and 2 g. salt (partly as subcutaneous normal saline). Raphael's serum chloride level on that day was 613 mg. per 100 ml. and Evelyn's 566 mg. per 100 ml. Electrocardiograms on both babies were normal.

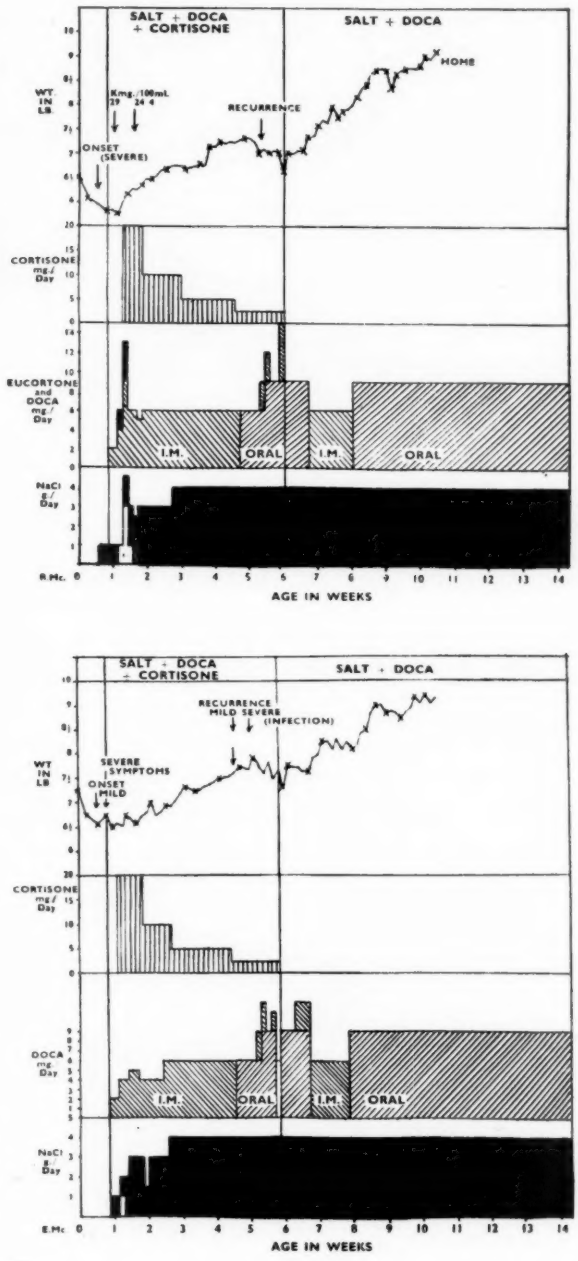

FIG. 2.—Progress charts of Raphael and Evelyn.

Clinically the electrolyte upset was still not controlled in either twin, the symptoms being much more severe in Raphael.

In view of the increasing amounts of salt and D.O.C.A. required with only temporary clinical improvement, it was decided to give cortisone, and both babies received 20 mg. intramuscularly on the evening of the ninth day. By the next morning both had gained weight, and, although still vomiting occasionally, looked very much better. Cortisone, 20 mg. daily, was continued for five days, was then gradually reduced and discontinued after 32 days.

Meanwhile the twins were stabilized on 4 g. extra salt per day given as a concentrated solution in the feeds, and 3 mg. D.O.C.A. intramuscularly twice daily. Weight gain was satisfactory, and vomiting had ceased. At no time was there evidence of oedema.

Oral D.O.C.A. in the form of sublingual pellets was later substituted for the intramuscular preparation in the same dosage. This resulted in a recurrence of symptoms and additional intramuscular D.O.C.A. had to be given at first. Evelyn, who at that time had a mild upper respiratory infection, was more severely affected. The recurrence of symptoms coincided with the withdrawal of cortisone and may in part have been due to this.

After increasing the dose of oral D.O.C.A. to 9 mg. per day the babies remained symptom free and gained weight satisfactorily.

They were discharged home at 2½ months of age. Progress thereafter was good, but was interrupted in Raphael at 3 months by an episode of vomiting associated with an upper respiratory infection requiring readmission to hospital. The serum chloride level was 449 mg. per 100 ml. Extra salt and intramuscular D.O.C.A. were given for some days but the baby was subsequently stabilized on the same doses as before and discharged home.

At 5 months the diagnosis was confirmed at The Hospital for Sick Children, Great Ormond Street, by endoscopy under anaesthesia and estimation of the urinary 17-ketosteroids in Raphael. These amounted to 4·85 mg. in 24 hours.

Both twins then remained well, and at 7 months Raphael weighed 15 lb. 1 oz., and Evelyn 16 lb. 5 oz. Both had two teeth and could sit unsupported.

Two weeks later they both developed Sonne dysentery and were admitted to a fever hospital. The progress of the illness was very stormy. The twins were finally transferred to the Gastro-enteritis Unit of the Queen Elizabeth Hospital for Children and, after repeated intravenous therapy and subsequent stabilization on 1½ mg. intramuscular D.O.C.A. and the equivalent of 4 g. extra salt per day, they were returned to the Whittington Hospital.

Intramuscular D.O.C.A. was gradually changed to the oral preparation in propylene glycol 3 minims t.d.s. (equivalent to 3⅓ mg. per day), and the extra salt intake was increased to 6 g. per day.

At 9½ months Raphael had a transient recurrence of symptoms requiring a temporary increase in the dosage of D.O.C.A., this time associated with suppurative otitis media.

At 10 months Raphael weighed 14 lb. and her blood pressure was 100/70 mm. Hg and Evelyn weighed 15 lb. 5 oz. and had a blood pressure of 90/60 mm. Hg.

Serum electrolytes were as follows:

Serum sodium	Raphael	275	mg. per	100 ml.
,, ,,	Evelyn	270	,,	,,
,, potassium	Raphael	24·2	,,	,,
,, ,,	Evelyn	24	,,	,,
,, chloride	Raphael	440	,,	,,
,, ,,	Evelyn	472	,,	,,
Fasting blood sugar	Raphael	70	,,	,,
,, ,,	Evelyn	60	,,	,,

Both twins were well except for hypochromic anaemia, which responded to iron therapy, in Raphael, and for eczema of the face in both, more severe in Raphael. Weights were extremely variable and on the whole stationary.

In order to try to prevent the recurrence of symptoms of adrenocortical insufficiency as a result of possible infections in the future, cortisone was again started, at first intramuscularly in a dosage of 25 mg. per day, and later orally in a dosage of 5 mg. four times a day. Urinary 17-ketosteroids gradually fell to 1·1 mg. in 24 hours and 2 mg. in 24 hours in Raphael and Evelyn respectively, and at 10½ months the twins were discharged home, to be readmitted at intervals for estimation of the urinary 17-ketosteroids.

Progress thereafter was excellent, and at 12 months Raphael weighed 17 lb. and Evelyn 18 lb. 6 oz. Both were again sitting without support. Both had six teeth. The bone age was normal. The eczema had completely resolved.

Later, cortisone was increased to 25 mg. per day, after which the urinary 17-ketosteroid excretion was 1·3 and 0·9 mg. in 24 hours in Raphael and Evelyn respectively. Both babies lost weight and therefore cortisone was reduced to the former dosage of 20 mg. per day. Thereafter, weight gain was once more satisfactory.

Discussion

In these babies cortisone appears to have been the main factor preventing death from adrenocortical failure in the neonatal period. Cortisone was discontinued after one month since it was at first thought possible to maintain the electrolyte balance adequately by the addition of salt and D.O.C.A. alone. It was also thought possible that the deficiency of salt-and-water-regulating hormones might prove to be only temporary as in the case reported by Doxiadis.

At that time it was decided to bring the children up as boys, since is is generally held that these patients, who develop early signs of virilism, adjust better both socially and psychologically if reared as boys from the start (Hinman, 1951).

In view of the frequent reappearance of symptoms of adrenocortical decompensation associated with

intercurrent infections in these twins, cortisone was given again at 10 months. By analogy with adult cases of Addison's disease, it was thought more possible thereby to prevent future crises. In addition, Crigler *et al.* (1952) in their detailed study of three cases, have shown that although clinically progress can be satisfactory on salt and D.O.C.A. alone, the serum chemistry cannot be maintained constantly normal without cortisone.

Apart from helping to maintain the electrolyte balance, cortisone suppresses the excessive production of androgenic hormones by the adrenal cortex. The four children so far treated with cortisone have not yet survived long enough for any assessment of its effect on their growth and sexual development. However, in patients with the adrenogenital syndrome alone, cortisone given in adequate doses has been shown to prevent masculinization and excessive bone growth successfully (Wilkins, Crigler, Silverman, Gardner and Migeon, 1952). It is, therefore, probable that the twins will now develop as girls, and if so, plastic surgery to the genitalia will have to be considered in the future.

Wilkins (1948) showed that for adequate suppression of androgenic hormone secretion, the dosage of cortisone should be the minimal amount which will maintain the daily urinary excretion of 17-ketosteroids below 1 mg. in infants, and between 1 and 3 mg. in children between 1 and 2 years. In the twins it was possible to reduce the daily urinary 17-ketosteroid excretion to 1·1 and 2·0 mg. at a daily dosage of 20 mg. of oral cortisone, and at the same time to maintain an adequate weight gain. When cortisone was increased to 25 mg. per day in an attempt to suppress the secretion of androgens further the babies lost weight. This was taken to be a sign of overdosage, and the amount given was again reduced.

During the initial period of control of the adrenocortical failure with salt and D.O.C.A., and during subsequent phases of adrenocortical decompensation associated with intercurrent infections, the most useful guide to treatment has been the clinical appearance and behaviour of the children. Biochemical estimations were used mainly to confirm the diagnosis of salt-and-water hormone insufficiency. In the day-to-day management of these children it is not justifiable to await results of serum chemistry estimations before initiating treatment.

Vomiting was found to be the first symptom of adrenocortical failure every time. Its cessation and a satisfactory weight chart were reliable evidence of adequate dosage of salt and D.O.C.A.

Summary

Female pseudohermaphroditism with adrenocortical failure in identical twins is described.

Cortisone was the main factor preventing death in the neonatal period.

Treatment with salt and D.O.C.A. was guided by clinical assessment rather than by biochemical estimations.

When stabilized on salt and D.O.C.A. alone, symptoms of adrenocortical failure reappeared in association with intercurrent infections.

Cortisone was started again and continued, primarily with a view to maintaining more adequately the electrolyte balance, so far with gratifying results.

Cortisone should make it possible for the babies to develop as females.

I should like to thank Mr. Innes Williams for his help in establishing the diagnosis, and Dr. Young and the staff of the Queen Elizabeth Hospital for Children for their expert care of these babies during a very severe illness. I am very grateful to Dr. Dorothy M. Parkin, of the Lister Institute, for the haematological investigations, to Miss Mason for supplying the photograph and reproducing the charts, and to the laboratory and nursing staff of the Whittington Hospital for all their assistance.

Special thanks are due to Dr. Simon Yudkin for permission to publish these cases and for his help in the preparation of this paper.

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EPILOIA AND ENDOCARDIAL FIBRO-ELASTOSIS

BY

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There has been some revival of interest recently in the condition known formerly as 'foetal endocarditis', and now as endocardial fibro-elastosis, and the subject has been well reviewed by Gowing (1953). It is believed to be characterized by progressive heart failure in infants and young children, presenting at necropsy cardiac hypertrophy and endocardial thickening produced by an increase in its fibrous and elastic tissue constituents.

The purpose of this communication is to record two cases of epiloia in which similar endocardial fibro-elastosis was found at necropsy. Two other cases of epiloia, in a series of 120 necropsies upon mentally defective children of lower grade, were without this change.

Case Reports

Case 1. The patient was illegitimate with a normal half-sister, three years older. Nothing is known of the father, but the patient's mother and her family had no neurological or mental disease. The mother was an unskilled factory hand, poor, with housing and domestic difficulties. During the pregnancy she was admitted to hospital for 'kidney trouble' well before confinement, remained an in-patient for three months following it, and died some months later. No further details are available.

Delivery was by lower segment Caesarean section. A week after birth it was noticed that the infant could not swallow and a throat swab was positive for diphtheria. The patient's backwardness was observed in early infancy. He sat up at 3 years but did not smile, walk or talk. At 7 months he was vaccinated and the first epileptic fit was seen then. The fits were frequent in later years, some being described as grand mal and others as petit mal, and he remained mentally an unresponsive idiot. At 10 years he had a prolonged respiratory illness diagnosed as an unresolved pneumonia or, possibly, tuberculosis. Shortly before his death from bronchopneumonia at 14 years, early adenoma sebaceum was noticed on his face and the diagnosis of epiloia was made.

PATHOLOGICAL FINDINGS. There was gross emaciation with pigeon chest. Barely visible adenoma sebaceum was present on the face without other skin lesions.

The heart was somewhat enlarged, weighing 202 g. Several flat lipomata were present on its surface near the apex penetrating well into the substance of the myocardium. The left ventricle was hypertrophied (Fig. 1), its wall measuring 2·1 cm. in its thickest portion. The endocardium was thickened in the left auricle, near the left ventricular surface of the inter-ventricular septum, and also over some of the chordae tendineae of the mitral valve. A firm oval nodule (Fig. 2) measuring 8 × 5 mm. projected into the right ventricle from the endocardium, and multiple irregular pale areas of tissue varying in size from less than 1 mm. up to 4 mm. could be seen within the heart muscle.

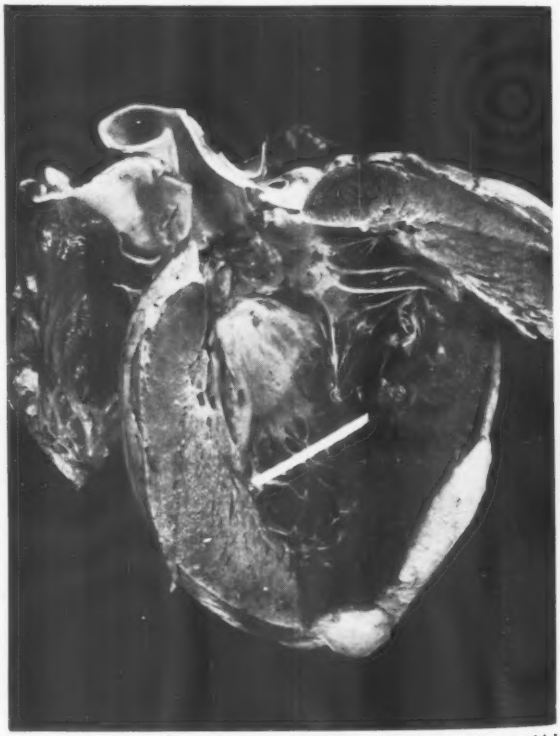

FIG. 1.—The left ventricle is hypertrophied, the endocardium is thick and opaque. Lipomata are present in the lower part of the heart.

FIG. 2.—Purkinjeoma projecting into the right ventricle.

The right lung was firmly adherent to the chest wall, and the cut surface of both showed a pattern of oedema, consolidation and lobular collapse. Fairly numerous tubercles were also found in both lungs and there was, in addition, peripherally in the upper part of the right middle lobe an area 5 × 3 cm. comprising many contiguous and fairly large cysts with more widely scattered smaller discrete cysts (Fig. 3).

The brain (1,410 g.) and other parts of the central nervous system were of normal size with no macroscopic abnormality. Numerous hard nodules were palpable, however, within the cerebral hemisphere and these became visible later after formalin fixation and the removal of the meninges, as somewhat pale portions of the gyri with a coarsely granular surface. An x-ray photograph of the brain showed that many of them were calcified (Fig. 4). Many white, hard, elongated and tortuous nodules—'candle gutterings'—were seen projecting into the lateral ventricles when the brain was cut in coronal sections (Fig. 5).

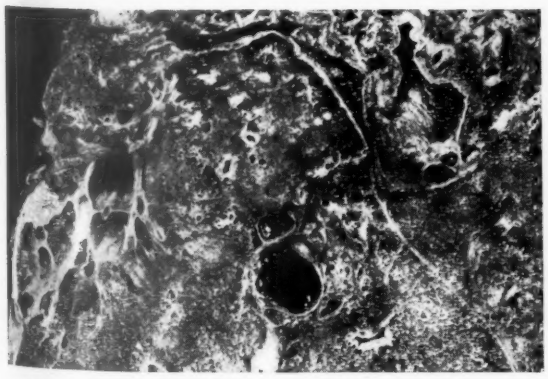

FIG. 3.—Large contiguous and smaller discrete cysts in the right lung.

MICROSCOPICAL EXAMINATION. All organs were fixed in formalin and later embedded in paraffin and celloidin, frozen sections being also used for fat staining and silver impregnation. The customary general and neurological staining methods were employed and some of these will be indicated below together with the relevant findings.

FIG. 4.—Radiograph of the brain showing dilatation of the ventricles and calcified nodules.

The larger nodules were well seen in Nissl sections of the brain as pale areas in which cortical lamination was obliterated (Fig. 6). Corresponding sections stained by the Holzer method showed the lesions as dark foci of dense fibrous gliosis in the cortex with or without extension into the subjacent white matter. More discrete nodules were also present in the centrum semiovale. The nodules were distributed evenly and in a seemingly haphazard manner throughout the cerebral hemispheres.

The nerve cells were greatly reduced in the cortical lesions, those remaining being pyknotic, shrunken and, frequently, orientated at unusual angles. Many nerve cells stained very faintly while others were abnormally large. Silver impregnation, such as Bielschowsky's, showed numerous tortuous or angular fibrils running from the cells at unusual angles and in many different directions. The glial cells were increased in number, most of them being fibrillary astrocytes. Other glial cells had

FIG. 5.—Subependymal nodules of 'candle guttering' in the lateral ventricle.

protoplasmic cytoplasm with irregular cell outlines. Some of the latter were distinguished by their strikingly large size (Fig. 7), homogeneous opaque cytoplasm and oval- or kidney-shaped nuclei which were peripheral and, sometimes, multiple. These cells were particularly numerous in the subcortical gliotic nodules. Microglial cells were also increased in number in some of the nodules. The silver impregnation methods, though effective, proved somewhat unreliable as a guide to the identity of the adventitious cells, methods recommended for demonstrating one type tending easily to impregnate others. It was, furthermore, impossible to decide for many of the abnormal cells whether their origin was glial or neuronal.

The myelin sheaths and axon cylinders were reduced in number within the affected areas and showed many degenerative changes such as beading, tortuosity and fragmentation.

The bulk of the gliotic nodules consisted of a dense irregular feltwork of glial fibres. The density varied from nodule to nodule and, within each, in a manner defying generalized description. Many possessed, however, three identifiable zones of gliosis: a superficial one occupying a layer 2-3 mm. in depth parallel with the cortical surface, an intermediate one of equal depth in which gliosis was less dense, and a third deep one which extended for a variable distance into the underlying white matter.

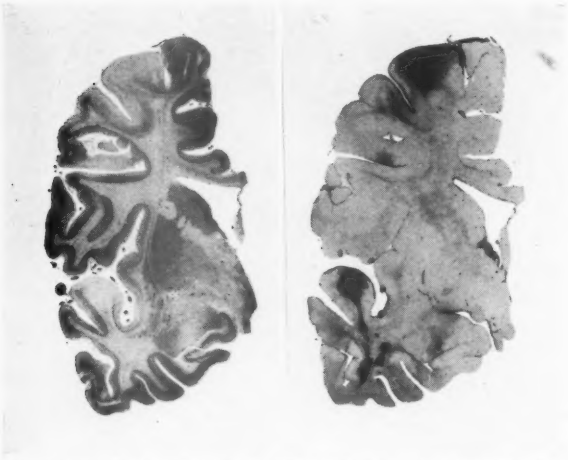

FIG. 6.—Coronal section of the left cerebral hemisphere stained by the Nissl method, left, and Holzer method, right. Obliteration of cortical pattern and areas of dense fibrous gliosis.

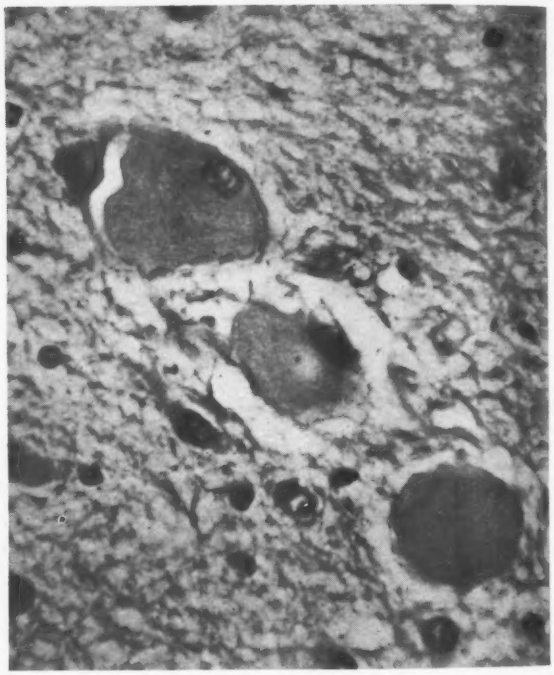

FIG. 7.—Large globoid cells in gliosed nodules of white matter. Haematoxylin and eosin × 500.

Many round or oval calcified granules, 15-20μ in diameter, were present in the gliotic nodules, particularly numerous round some of the blood vessels.

The histological structure of the subcortical nodules did not differ substantially from that of the cortical ones save for the absence in the former of readily identifiable nerve cells though some contained a few large adventitious cells the identity and origin of which was doubtful.

The subependymal nodules of the 'candle guttering' were distinguished by their cellularity, many of their cells being rather uniform, large and elongated with oval or kidney-shaped vesicular nuclei and cylindrical or tapering cytoplasm. Some small, festooned ependymal nodules

FIG. 8.—Festooned nodule projecting into the ventricle. Haematoxylin and Van Gieson. × 120.

were also present in the ventricles and these contained dense glial fibres and uniform fibrillary astrocytes (Fig. 8).

In addition to the characteristic areas of gliosis described above, diffuse fibrous gliosis without marked demyelination or cellular change was present in the marginal layers of the cerebrum away from the nodular lesions, around the periphery of the brain-stem and spinal cord, around the inferior olives and the gray matter of the spinal cord and in parts of the molecular layer of the cerebellum. The latter showed also some atrophy of the Purkinje and granular layers.

The thickened endocardium consisted of rather acellular strands of collagen interspersed by reticular elastic tissue (Fig. 9). While the fibro-elastosis was confined to the endocardium over the greater part of the affected area, the subjacent muscle was also involved in it in a few places.

The nodule projecting into the right ventricle and the pale smaller areas situated within the heart muscle were found to be identical with the debatable structures usually referred to as 'rhabdomyomata'. They consisted of a solid mass of large cells each of which had a round central nucleus and cytoplasm which was either entirely absent or else arranged in radial or tangential fibrils and bundles of fibrils. Some of the latter showed distinct transverse striation particularly when stained with Heidenhain's haematoxylin (Fig. 10). In addition to the tumour-like proliferation of these cells in the situations

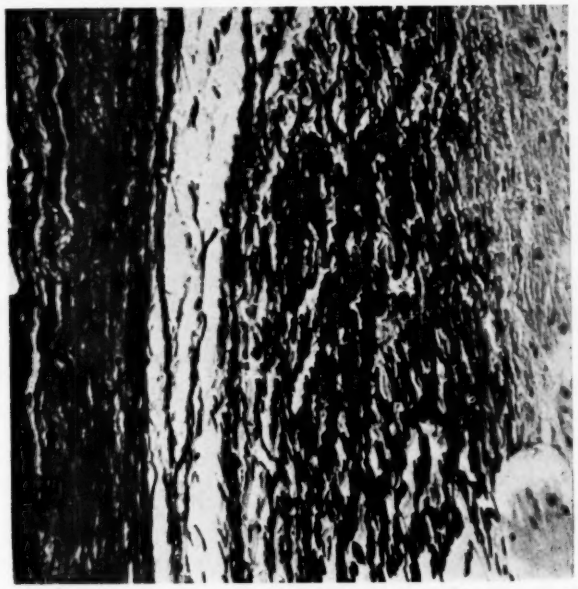

FIG. 9.—Fibro-elastic tissue in endocardium and subjacent muscle. Verhoeff's elastic tissue stain and Van Gieson. × 120.

described above, they were also distributed singly or in small clusters under the fibro-elastic layer of the endocardium and within small irregular areas of fibrous tissue in the heart muscle itself.

The large lipomata seen on the surface of the heart were formed by adipose tissue of normal appearance.

FIG. 10.—Large 'empty' cells of Purkinjeoma with transverse striation near the cell border. Heidenhain's haematoxylin. × 180.

Sections of the facial skin taken from the area of adenoma sebaceum showed some hyperkeratosis and irregular thickness of the Malpighian layer. The rete pegs lacked uniformity; many were excessively long and thin, others were flattened. The dermis was thickened owing mainly to an increase in its fibrous tissue. There was also some increase in the number and size of the sebaceous and sweat glands.

Many of the tuberculous lesions in the lungs showed caseation beginning in the centre. The areas of pneumonic consolidation contained polymorphonuclear leucocytes with numerous phagocytic cells, having granules and globules of albuminous or fatty material within their cytoplasm. Some of these phagocytic cells were multinucleated. Other sections of the lungs confirmed the naked-eye impression of lobular collapse and oedema. The cystic cavities mentioned in the naked-eye description of the lungs were twofold in structure. Some were bronchiectatic having walls formed by fibro-muscular tissue, mucous glands, fat and cartilage and lined by a single layer of columnar ciliated epithelium. Others were greatly dilated venous spaces. Lymphatic tissue within the cystic area contained a few tuberculous lesions. These were, however, like the other tuberculous lesions discrete, and the cystic cavities did not appear to be secondary to tuberculosis.

Case 2. The patient, the only child of young working class parents whose families were free of mental or nervous disease, was born after a normal pregnancy and confinement, and weighed 6¾ lb. A naevus measuring 1 × 2½ cm. was present upon her left lower eyelid but she appeared otherwise normal. She had an epileptic convulsion at the age of 4 months when she was seen to clench her fist and her body to stiffen. Fits recurred frequently after that, some being described as major and others as minor, and she had, in addition, frequent prolonged screaming attacks. She was slow in passing the normal landmarks of development and remained incontinent of urine and faeces. At the age of 4, on admission to the Fountain Hospital, a few pink spots were seen on her face as well as the naevus. A radiograph of the skull showed no intracranial calcification and the condition was diagnosed as epiloia or central neurofibromatosis. She could hear loud noises and see objects but did not react to speech and no contact could be established with her. She was hyperactive in her cot, exhibiting purposeless movements of head and limbs. She was able to take food to her mouth but remained completely incontinent and tended to eat faeces. Her tendon reflexes were normal. The psychologist's report read as follows:

'She was restless and moved around her cot continually; she could sit, stand and walk alone. She turned to investigate the sound of a bell, grasped it and rang it herself. She showed no dominant handedness. It was not possible to determine whether she understood anything that was said to her. She made no attempt to imitate the construction of a tower or any other simple activity, but handled the bricks and ball in aimless fashion. She made no attempt to talk but uttered harsh cries and grunts. Her developmental age on the Vineland Maturity Scale is approximately 9 to 10 months and she would appear to be of idiot-imbecile level.'

The patient died two months after admission following respiratory illness.

PATHOLOGICAL FINDINGS. The body was that of a very thin girl with many excoriations on both forearms and hands. The facial naevus could be recognized but not the adenoma sebaceum.

The heart was normal in size (65 g.), several small lipomatous nodules being present upon the epicardium. The endocardial surface of the left auricle and of the left side of the interventricular septum were somewhat thickened and opaque, this change being less marked than in Case 1. A hard, indurated area of fibrous tissue replaced, in addition, the endocardium, the columnae carneae and part of the myocardium at the apex of the left ventricle.

The trachea and bronchi were inflamed and the cut surface of the lungs showed bronchopneumonia and a number of small abscesses.

Some small cysts measuring up to 2 mm. in diameter were present upon the surface of the kidneys. The renal cut surface revealed the presence of many irregular areas up to 8 mm. in size in which the normal pattern was replaced by uniform white homogeneous tissue.

The meninges were greatly congested. Many irregular hard nodules were palpable in the brain, which was normal in size (1,290 g.). They were more numerous than in Case 1, leaving little of the intervening cerebral substance free and of normal consistency. These nodules showed themselves, once more, as paler and coarser portions of the gyri after the brain was fixed and the meninges stripped. 'Candle guttering' was likewise present in the lateral ventricles.

Numerous small areas in which brain tissue was replaced by somewhat translucent, gelatinous, greyish material were seen in the white matter of the cut brain. Most of these measured less than 1 mm. and were round, oval or lineal suggesting vascular or perivascular distribution; the largest measured 3 mm. in diameter.

The brain-stem, cerebellum or spinal cord showed no naked-eye abnormality.

MICROSCOPICAL EXAMINATION. The material was prepared as in the previous case and the histological findings being, in the main, identical, attention will be given in the description below to changes differing from those in the former.

The cortical gliotic nodules had a greater number of large adventitious nerve cells (Fig. 11). Although, as mentioned already, no calcification was seen on x-ray examination, many calcified particles were, nevertheless, present in the nodules, particularly, the subependymal ones of 'candle guttering'.

In contrast to the first case, some gliotic nodules were also present in the reticular substance of the medulla and in the cerebellum, being situated, within the latter, in the most peripheral portions of its middle lobe. These cerebellar nodules consisted of a dense proliferation of fibrous glia in the molecular layer with a relatively slight increase in astrocytes. The Purkinje cell layer was

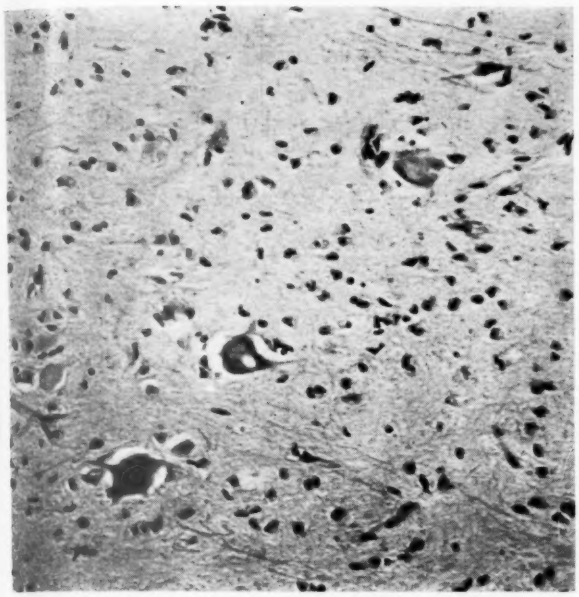

FIG. 11.—Cerebral cortex showing large distorted nerve cells and an increased number of glial cells. Haematoxylin and Van Gieson. × 180.

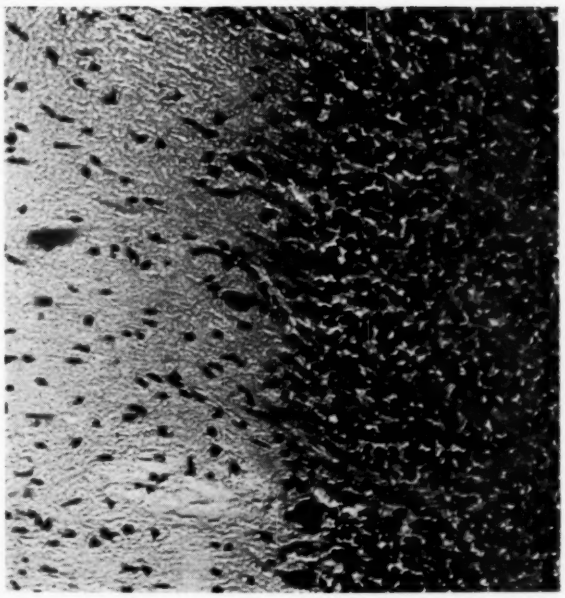

FIG. 12.—Cerebellum with abnormal Purkinje cells. Haematoxylin and eosin. × 180.

FIG. 13.—Perivascular reticulation of cerebral white matter. Haematoxylin and Van Gieson. × 180.

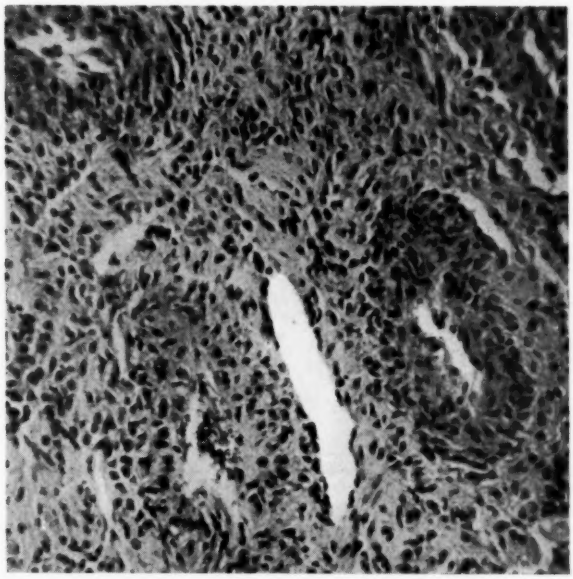

FIG. 14.—Endothelio-fibroma of kidney. Haematoxylin and eosin. × 180.

occupied by a large number (Fig. 12) of elongated large cells set in palisade fashion next to each other. These appeared to be modified Purkinje cells, as it was possible to trace transitional forms between the two types at the junction of the gliotic and normal tissue. The granular layer showed considerable atrophy and gliosis while the white matter was almost completely replaced by glial tissue.

The 'gelatinous' foci of the cerebral white matter presented as areas of perivascular reticulation, lacunation and adventitial hypertrophy (Fig. 13). The normal tissue around the blood vessels was replaced by a loose network of collagen and reticulin fibres, with a few compound granular corpuscles lying within its meshe:. Some of the blood vessels in the centres of the affected areas showed hyaline degeneration.

The endocardial changes were similar but less marked than in the first case. Although not visible to the naked

eye, microscopical clusters and nodules of 'rhabdomyomatous' heart cells were present under the endocardium and within fibrotic areas situated between myocardial fibres.

Examination of the lungs confirmed the naked-eye findings of bronchopneumonia and suppuration.

The abnormal tissue in the kidneys was formed by a solid mass of rather uniform spindle-shaped or curled cells with vesicular or rod-shaped nuclei (Fig. 14). The blood vessels of this tissue had greatly thickened walls

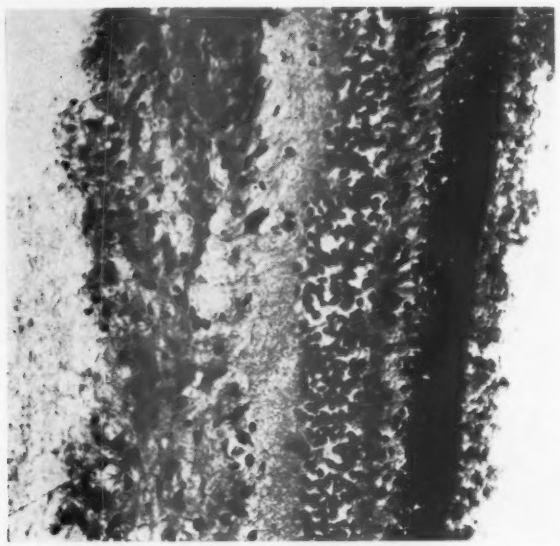

FIG. 15.—Phakoma of the retina in layer of optic nerve fibres. Haematoxylin and eosin. × 180.

consisting of several irregular layers of cells resembling the above. Some collagen and reticulin were also present between the cells, and the 'tumours' could, perhaps, be best described as endothelio-fibromata.

While no phakomata were seen on naked-eye inspection of the retinae, they were present in the histological sections as irregular flattish accumulations of rather uniform glial cells in the layer of optic nerve fibres (Fig. 15).

Discussion

Fibro-elastosis. The findings in Case 1 were characteristic of endocardial fibro-elastosis; they were definite if less pronounced in Case 2. This association of fibro-elastosis with epiloia has already been mentioned by me in a discussion of the structural features of epiloia (in press) and included in the list of lesions occurring in this condition (Table 1). Fibro-elastosis appears to have been also present in at least two of the previously recorded cases: in Case 15 of the series reported by Critchley and Earl (1932) and in the case published by Norman and Taylor (1940). Further cases of this association may have been easily overlooked, especially as most published accounts of epiloia make little or no mention of organs other than the brain, and it may well be that it will be found more frequently if attention is paid to it in future studies.

Endocardial fibro-elastosis was also sought in association with other conditions in the current series of necropsies and found in two cases of gargoylism and one of dermatomyositis. It is also noteworthy that Henderson, Macgregor, Thannhauser and Holden (1952) seem to have recorded a similar change in the series of gargoylism reviewed by them. They write:

> 'The endocardium had a normal appearance in most of the specimens, but in six it was thickened and opaque: in one case this change was apparently generalized, in another it was limited to the left auricle, in two to the left ventricle, and in one to both ventricles.'

Thus it would seem that endocardial fibro-elastosis, even when it is marked, cannot be regarded as a disease in itself even though there are certain cases in which it is the sole significant abnormality at necropsy. It is suggested, therefore, that the designation, 'endocardial fibro-elastosis', be used to imply a non-specific structural change rather than a disease entity as such.

EPILOIA

Brain	Skin	Heart	Kidney	Bones
*1. Tuberous sclerosis	*1. Adenoma sebaceum	*1. Rhabdomyoma (Purkinjeoma)	*1. Mixed benign tumours	1. Periosteal nodules
*2. Candle guttering	2. Peau de chagrin	2. Lipoma. Fibroma	2. Rare malignant tumours, e.g., carcinoma or sarcoma	2. Osteoporosis
3. Glioma	3. Flat warts	3. Fibro-elastosis	3. Polycystic kidney	3. Cysts
4. Secondary changes, e.g., demyelination, softening, etc.	4. Haemangioma		Teratoma	4. Melorheostosis
	5. Fibroma			5. Bony surface excrescences
	6. Subungual fibroma and haemangioma	Lungs	Other Organs	
Eye	7. Vitiligo	1. Congenital Cysts	Haemangioma and benign tumours have been mentioned in thyroid, spleen, thymus, breast and duodenum	Skeleton
*1. Phakoma	8. Leucoderma	2. Alveolar cell adenoma		1. Spina bifida
	9. Café au lait spots			2. Syndactyly, polydactyly

* Common lesions.
Others, rare lesions.

Perivascular Reticulation. The perivascular lacunation and adventitial hypertrophy in the white matter has been previously discussed by Naidoo (1952) in his account of two cases of gargoylism but has not been observed in epiloia. Its occurrence in one of the present cases is therefore of interest.

Nature of 'Rhabdomyoma'. The nature of the cardiac lesions which are customarily described in the literature as 'rhabdomyomata' is still debatable (Prichard, 1951). I have compared the histological sections of the present cases with the endocardium and myocardium of horses which show numerous normal Purkinje cells and fibres. The similarity between the latter and those in the heart lesions of epiloia is very striking in every respect: situation, size, vacuolation and transverse striation of cytoplasmic bundles. The term 'Purkinjeoma' rather than 'rhabdomyoma' appears therefore more appropriate for the tumour-like accumulation of these cells.

Summary

Two cases of epiloia showed endocardial fibro-elastosis in addition to more familiar changes in the brain and other organs. This association is discussed and it is suggested that the structural change, fibro-elastosis, may occur in a number of conditions other than the disease bearing that name, and is not necessarily a disease *sui generis*. Perivascular reticulation and adventitial hypertrophy were present in the cerebral white matter of one of the cases, a finding not hitherto recorded in epiloia.

I am greatly indebted to my lay and medical colleagues at the Fountain Hospital for their cooperation and access to case records. Mr. J. F. Watt and Mr. J. E. Stevens have assisted in the histological and photographic work.

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BACTERIAL ENDOCARDITIS COMPLICATING SEPTICAEMIA IN AN INFANT

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Septicaemia in the first few months of life is still unfortunately a relatively common condition, but the introduction of antibiotics has altered the prognosis dramatically. However, certain factors, such as a failure to reach a diagnosis, or an unusually virulent or resistant organism, may result in death.

Bacterial endocarditis is a rare complication of septicaemia in infants, and the existing descriptions are, in general, unsatisfactory because of insufficient bacteriological and pathological detail (Morison, 1952).

Sansby and Larson (1930) gave several references from the German literature of between 50 and 70 years ago and they also collected more recent reports on cases of bacterial endocarditis occurring in infants, but most of these were incomplete. Their own case was supported only by macroscopic descriptions of the heart and the causative organism was not named.

Since this paper, D'Ewart (1931) recorded a case of a 13-day-old infant with a staphylococcal septicaemia. The heart lesion was on the posterior wall of the right ventricle near the pulmonary valve. Brandes (1933) reported the occurrence of gonococcal tricuspid endocarditis in a 10-day-old infant. Plaut and Sharnoff (1935) and Plaut (1939) added two further cases but in neither was an organism found. The first of their cases occurred in a premature foetus, a small vegetation being discovered on a mitral valve cusp. In the second case, a day-old infant with a tricuspid valvular lesion, there were additional factors such as two possibly infected ante-mortem venous thrombi and a subarachnoid haemorrhage.

In an interesting paper Wolff (1940) reviewed the continental, American and British literature before giving details of two infants aged 3 months and $3\frac{1}{2}$ months, diagnosed on clinical grounds as suffering from bacterial endocarditis. Both survived the acute illness, which was attributed to a staphylococcal skin infection, only to be left with permanent cardiac damage.

Since the advent of the antibiotics no further case reports have been traced, and, in view of this rather scanty and often unsatisfactory literature, the following case is recorded.

Case Report

C.G., a boy, the second child of healthy, unrelated parents, was born by a low forceps delivery at term in an Edinburgh nursing home on August 29, 1952. His birth weight was 8 lb. 3 oz. He made normal progress until his ninth day of life when he became anorexic, listless and irritable. His condition deteriorated, and on September 9 he was admitted to the Royal Hospital for Sick Children, Edinburgh, aged 11 days.

When examined on admission, he was a toxic-looking, jaundiced infant. His state of hydration was poor and his tongue was flecked with bile-stained vomitus. The abdomen was distended and an area of induration surrounded an infected umbilical stump. The liver and spleen each extended about one inch below the costal margins. No other abnormality was found on clinical examination.

Table 1 and Fig. 1 give details of the temperature, body weight, number of stools and vomits, haematology and examination of urine.

TABLE 1
DETAILS OF BLOOD AND URINE EXAMINATIONS

Days after Admission	1	3	5	7	10	14	21	28
Blood								
Haemoglobin (Sahli) g. %	16·8	17·5	13·3	10·1		8·9	8·9	9·1
Total W.B.C. (per c.mm.)	7,800	14,000	22,600	17,000		31,400		29,000
Principal cell type	Neut.	Neut.	Neut.	Neut.		Neut.		Neut.
Urine								
Albumin	++	+			—		—	
Bile	+	Trace			—		—	
Microscopical findings	N.A.D.	N.A.D.			N.A.D.		N.A.D.	

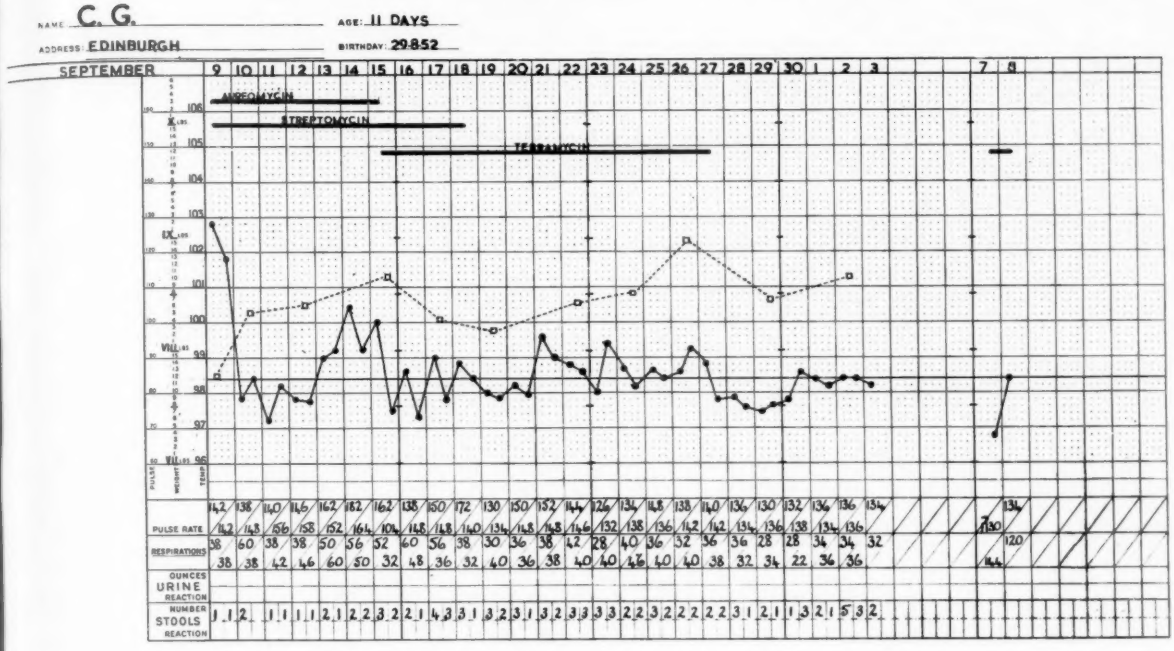

FIG. 1.

Therapy was begun immediately a clinical diagnosis of septicaemia had been made. He was given streptomycin, 200 mg. twice daily intramuscularly, and aureomycin, 100 mg. six hourly orally.

The umbilical discharge was swabbed and yielded a growth principally of coagulase-positive *Staphylococcus aureus*.

During the first two days in hospital, despite the disappearance of fever, his condition deteriorated, oedema of the legs and sacrum developed, and, in addition to deepening jaundice, an extensive purpuric rash appeared on the trunk and limbs. Thereafter both the jaundice and purpura slowly faded although the oedema increased. Six days after admission he was free of jaundice but the oedema remained. As he was still feverish, terramycin, 50 mg. six hourly orally, was substituted for aureomycin. The infant began to improve steadily and the oedema slowly disappeared. The liver and spleen became smaller. He was discharged home on October 3, 24 days after admission, apparently in good health.

For two days he remained well, but then he began to vomit and became dyspnoeic during his feeds. He was anorexic. A systolic murmur was present over the whole of the praecordium but it was maximal at the apex. The apex beat was rather diffuse and it was in the fifth interspace about half an inch outside the mid-clavicular line. The infant was readmitted in the evening of October 7. In addition to the cardiac signs, the liver extended for about 2 in. below the costal margin and the spleen was again easily palpable. A blood culture taken on admission later proved to be sterile. Oxygen therapy and terramycin were given but the infant died suddenly next morning. A post-mortem examination was performed three hours later.

FIG. 2.—Section through the left ventricle showing the large vegetation on the cusp of the mitral valve.

ABSTRACT OF POST-MORTEM REPORT. Both pleural sacs contained an increased quantity of fluid. The lungs were firm and oedematous. The heart was increased to about one and a half times the usual size due to hypertrophy and dilatation of the right ventricle, and by dilatation of the left ventricle. Firmly adherent to the posterior cusp of the mitral valve and projecting into the left atrium there was a large elongated, firm mass of thrombus, about 2 cm. in length (Fig. 2). Smaller masses of thrombus were adherent to the other cusps. The cusps themselves were not obviously thickened, nor were the chordae tendineae shortened or thickened. The other valves of the heart showed no abnormality. The peritoneal sac contained an excess of clear fluid. The liver and spleen were both increased to about one and a half times the usual size, the result of a chronic venous congestion. Each kidney showed small, whitish, firm areas in the cortex, probably infarcts.

MICROSCOPICAL REPORT. The lungs, liver and spleen showed the typical features of chronic congestion. In the kidneys the presence of small cortical infarcts was confirmed. Sections of the mitral valve showed the cusps to be composed of granulation tissue (Fig. 3). On the surface was a mass of thrombus into which this granulation tissue was extending. Numerous clumps of Gram-positive cocci were evident throughout the thrombotic mass. In addition to the large thrombotic mass noted at necropsy, microscopy confirmed the presence of smaller vegetations on the other cusps, and in these the histological picture was similar. The tricuspid valve showed no abnormality.

FIG. 3.—Photomicrograph showing the attachment of the thrombus to the cusp of the mitral valve.

The pathologist concluded that this was a case of acute infective endocarditis, apparently altered as a result of antibiotic therapy, in which mechanical obstruction resulting from massive thrombus deposition on the mitral valve was an important factor in causing death.

Comment

This case presented initially with the characteristic signs of septicaemia. The infection appeared to be staphylococcal as this organism was grown from the umbilicus and Gram-positive cocci in clusters were seen in the section of the mitral valve vegetation.

The infant apparently responded to antibiotics and when he was discharged from hospital no cardiac abnormality was suspected. The clinical picture on his readmission four days later was that of congestive heart failure. The cause of the symptoms was only discovered at the post-mortem examination when the size and situation of the endocardial vegetation showed that there must have been intermittent obstruction of the mitral orifice.

I should like to thank Dr. D. N. Nicholson for permission to publish this case, Dr. A. D. Bain for the post-mortem summary, Mr. T. C. Dodds who kindly supplied the photomicrographs, and I am also very grateful to Professor R. W. B. Ellis for his helpful criticism.

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THE AGE OF CHILDREN WHEN GROWTH IN STATURE CEASES

BY

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The age at which the children in a community reach adult stature is usually determined from an estimation of the upper limit of the distribution of the age at which growth in height ceases. The mean statures for different age-groups are examined, and the age at which the upward trend in the mean values stops is taken as the upper limit of the distribution. Neither the mean age nor the standard deviation of the distribution can be obtained from such 'cross-sectional' data, and estimates depending upon the concept of an upper limit to a distribution are unsatisfactory for statistical reasons. However, these objections do not arise in the analysis of 'longitudinal' data, that is, observations on the same individuals recorded over a period of several years. In a survey of this kind, Morant (1952) found that 15·3% of Royal Air Force apprentices reached adult stature by their eighteenth birthday, and 32·1% by their nineteenth birthday. In the following paper, corresponding data for present-day school boys and girls are analysed.

Data

The records were placed at our disposal by the authorities of two independent or public schools in England, and it can be taken that the children concerned came from families in the upper income group of the community. The measurements were recorded at medical examinations of boys made in the period 1949 to 1952, and of girls during the period 1945 to 1952. Records of the stature of 75 boys until they were at least 18 years 6 months old were available. They were measured to the nearest quarter of an inch at the same time of the day and without clothing, at four-monthly intervals. Similar data for 67 girls, measured annually to the nearest one-eighth of an inch in gym clothing without shoes, were available until they were at least 17 years 7 months old. The anthropometers used in both series of measurements were of the type attached to weighing machines.

Analysis

The measurements of each child were charted and the records sorted into two groups; in one, growth in stature occurred between each examination, whereas in the other no increments were found for varying intervals of time. A detailed examination of the records in the latter group shows that two types of record occur. In the first, no further increase takes place during the period of observation, but in the second, after the stature has shown no change for some time, a further increase occurs. Figs. 1 and 2 show examples of the first type, and Figs. 3 and 4 of the second. It is difficult to define a practical standard which will determine when growth in stature has stopped, because the period of arrested growth in the second type of record may extend for two years or more. In this paper, growth is taken as complete for the boys when three similar consecutive measurements occur over a period of eight months, and for the girls when two consecutive measurements are recorded over a period of 12 months, differences of one-quarter of an inch or more being regarded as significant. Thirty-five boys and 26 girls continued growing until after the observations stopped, and 40 boys and 41 girls were classified as having stopped growing during the period of observation. In the latter group, the stature of 20 boys and 29 girls remained unchanged, and that of 20 boys and 12 girls showed an increase before the records stopped.

The age when growth is complete is taken to be midway between the last occasion when growth was in progress and the first occasion when it had stopped. In this way account is taken of the error introduced by grouping the data. For example, one girl grew until at 16 years 1 month her stature was 65 inches, and at both 17 years 1 month and 18 years 1 month it was 66 inches. Clearly she was growing at the age of 16 years 1 month and not at 17 years 1 month, so 16 years 7 months was taken as the age

FIGS. 1 and 2.—Records showing the growth process to be arrested. The number by each growth curve identifies the subject. Most records are of this type.

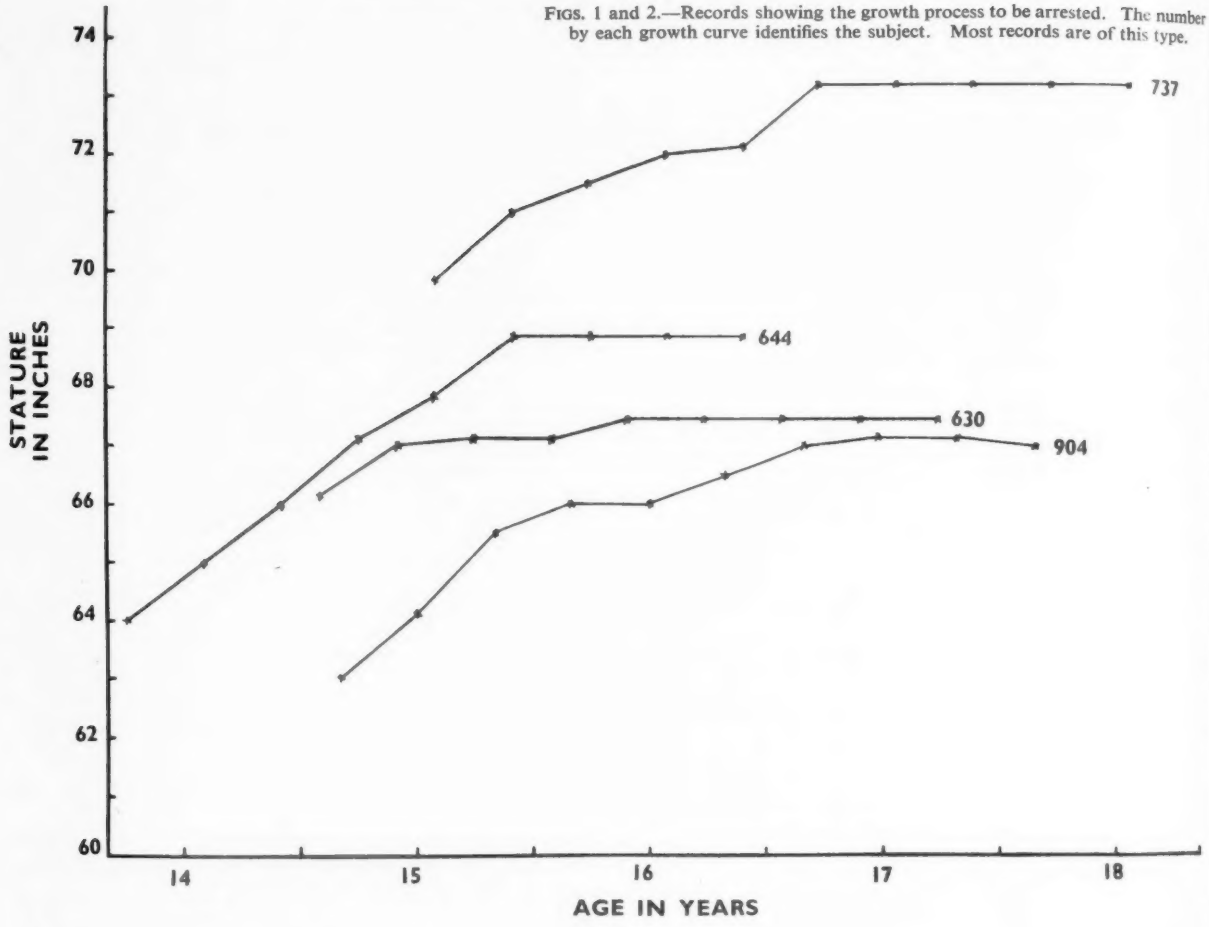

FIG. 1.

when growth in stature ceased. In this manner boys and girls, on the average, have the same stature for 10 and 18 months respectively before they are classified as having ceased to grow. It has been necessary to make this difference in the standard of classification for boys and girls, because of the limitations of the data, but in this case it will not invalidate the comparison of the results.

A few aberrant measurements were encountered. For example, some measurements were less than either the preceding or succeeding records, and occasionally a measurement was found to be larger than any later one recorded. These measurements have been attributed either to the effect of diurnal variation in stature, or to mistakes in technique, and have been disregarded.

The number of children in the samples who were still growing when the observations ceased have been combined with the observed frequencies of children who had stopped growing at earlier ages, and give a 'censored' distribution of the age at which growth in stature ceases. These censored data have been analysed by fitting a normal distribution by the method of Grundy (1952) and Hald (1952a and b).

Results

The observed frequencies of the age at which growth in stature stops in boys and girls are given in Tables 1 and 2 respectively. They are accompanied by the expected frequencies calculated on the assumption that the observations follow a normal (Gaussian) distribution. The agreement is good in both cases and statistical tests show that the observed frequencies do not deviate from the expected ones significantly (χ^2 for boys (d.f.4)$=4\cdot8$ and for girls (d.f.4)$=5\cdot8$). Thus the assumption that the observations follow a normal (Gaussian) distribution is a reasonable one. On the other hand, no observations exist in the upper part of the distribution, and complete data

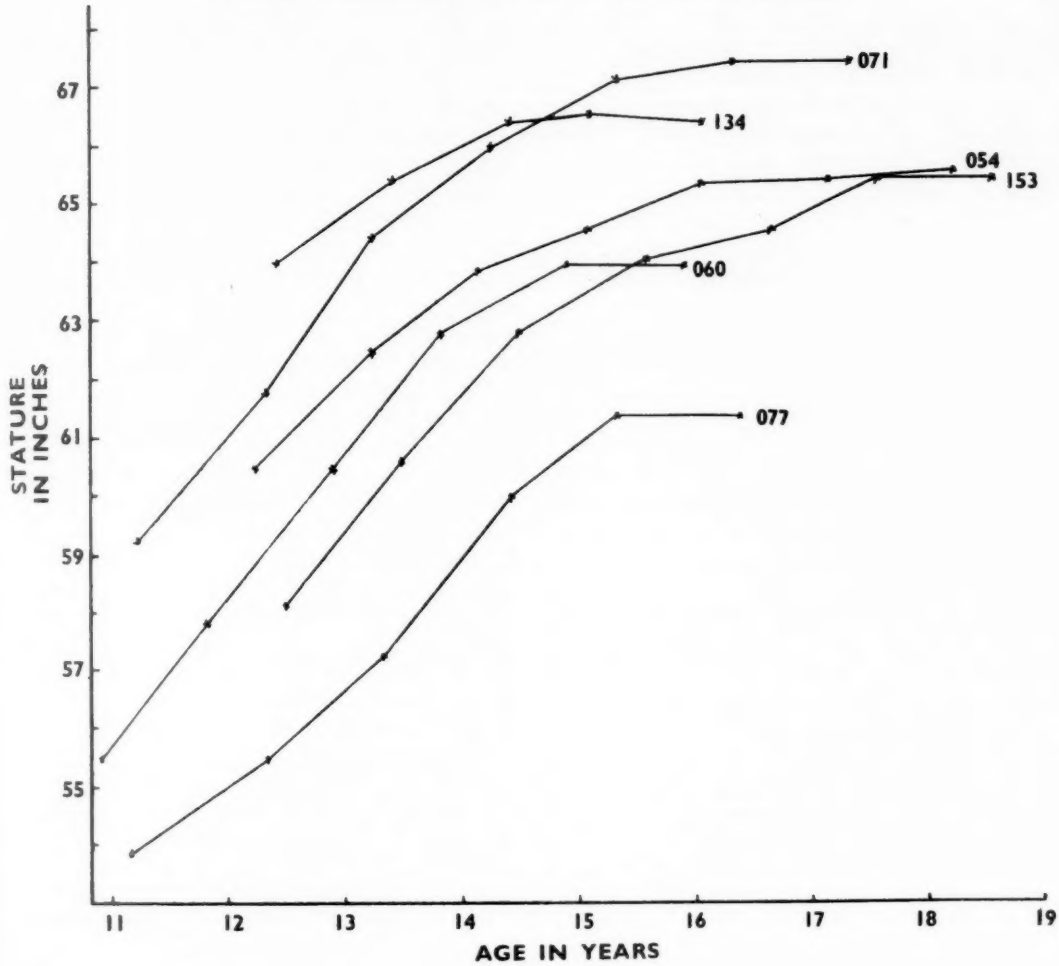

FIG. 2.

TABLE 1

OBSERVED AND EXPECTED FREQUENCIES OF AGE WHEN BOYS REACH ADULT STATURE

Age in Years and Months	Observed Frequency	Expected Frequency
17 11 and older	35	34·7
17 10 to 17 7	12	11·9
17 6 to 17 3	11	10·5
17 2 to 16 11	4	7·9
16 10 to 16 7	8	5·1
16 6 to 16 3	3	2·8
16 2 to 15 11	2	1·3
15 10 and younger	0	0·8
Total	75	75·0
Number observed to cease growth during period of observation	40	—

χ^2 (d.f.4) 4·8
Mean 17 years 9·08 months
s.d. 9·96 months

TABLE 2

OBSERVED AND EXPECTED FREQUENCIES OF AGE WHEN GIRLS REACH ADULT STATURE

Age in Years and Months	Observed Frequency	Expected Frequency
16 8 and older	26	25·2
16 7 to 16 2	10	11·6
16 1 to 15 8	8	11·0
15 7 to 15 2	11	8·6
15 1 to 14 8	9	5·6
14 7 to 14 2	3	3·0
14 1 and younger	0	2·0
Total	67	67·0
Number observed to cease growth during period of observation	41	—

χ^2 (d.f.4.) 5·8
Mean 16 years 2·71 months
s.d. 13·62 months

may show their frequency to be unusually high. If the distribution is skew with a long tail to the right, it will have a considerably higher upper limit and the mean will be increased, but since the data extend

beyond the 50% point, the estimates, considered as estimates of medians, should not be affected.

The analysis of the observations shows that the mean age of boys when they stop growing is 17 years 9·08 months ± 1·87 months and that the distribution has a standard deviation of 9·96 months. The corresponding age for girls is 16 years 2·71 months ± 3·44 months and 13·62 months respectively. For example, 5% of the boys and girls are expected to have stopped growing before the age of 16 years 4·75 months, and 14 years 4·37 months respectively, and as few as 5% of them would be expected to be still growing after the age of 19 years 1·42 months and 18 years 1·05 months respectively.

Discussion

The foregoing analysis shows that girls on the average stop growing in stature 18·37 months before boys and this result is consonant with the generally recognized fact that girls mature physically at an earlier age than boys. It is evident that growth in stature stops in 90% of boys within a period of 2 years 8·67 months, and in 90% of girls within a period of 3 years 8·68 months, and it is clear that girls show a greater variation in the age at which adult stature is reached than boys.

The only means of comparing the results for present-day children with information about children 80 years ago, is by estimating the upper limit of the distribution, because all the earlier information is based on this limit. The ages by which 99% of boys and girls will be expected to have stopped growing have been taken as a practical approximation to this limit. These ages are 19 years 8·29 months and 18 years 10·44 months respectively for boys and girls. The upper limit of the distribution in the upper socio-economic group 80 years ago was about 20 years 6 months and 19 years 7 months for boys and girls respectively (British Association for the Advancement of Science, 1883) or about nine or 10 months later than it is now. We have no information about the sampling variation of these estimates, but the differences are sufficiently great for there to be little doubt that, on the average, individuals in the upper socio-economic group reach adult stature at an earlier age now than in the past. This conclusion is supported by other evidence, such as the recent finding that Scotsmen of every social class ceased growing in stature before their nineteenth year in 1941 (Clements and Pickett, 1952). The change may be attributed either to a general tendency for all children to mature at an earlier age, or to a selective change limited, for example, to a reduction in the frequency of older children who are still growing, and it is uncertain which of these factors is the more important one. Evidence such as the fact that children aged from 5 to 13 years show, on the average, an advance in development of from 18 months' to two years' growth during the last 80 years (Clements, 1953) supports the former

FIGS. 3 and 4.—Records showing a later period of growth.

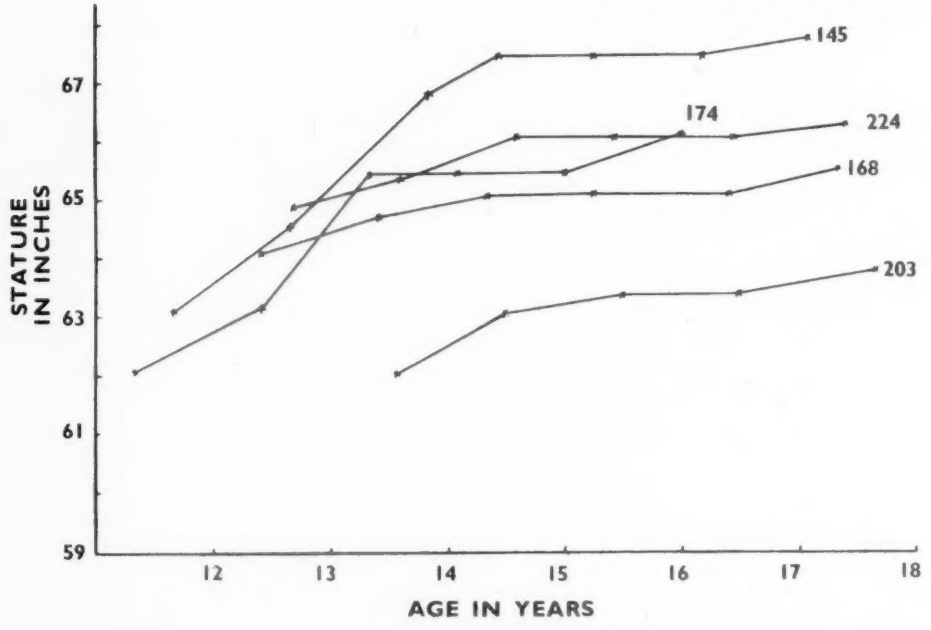

FIG. 3.

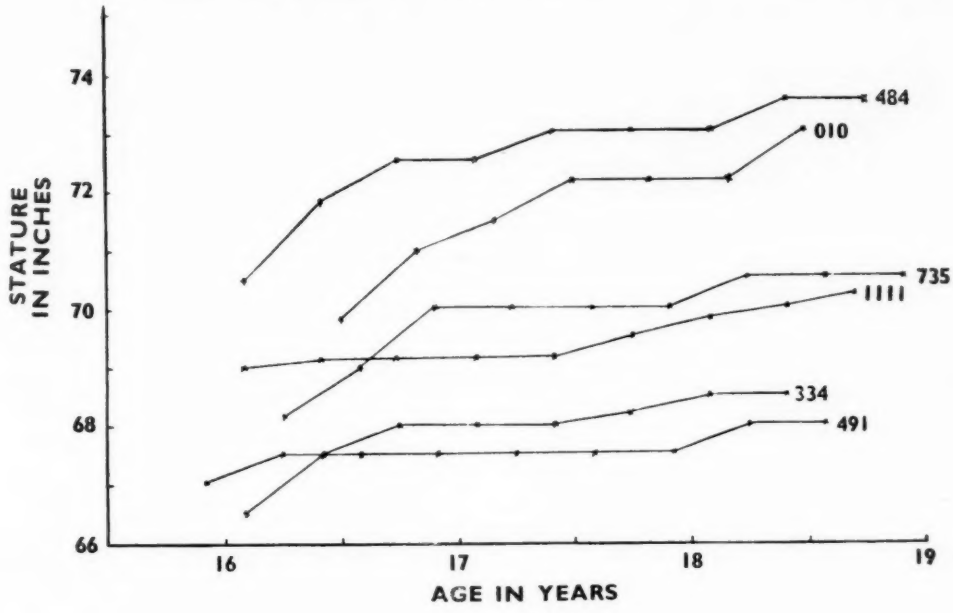

FIG. 4.

possibility, whereas the fact that growth in stature has been observed to begin again in a proportion of the older children following a long period of arrest—an observation also made by Morant (1952)—favours the latter explanation.

There is little doubt that the tendency for growth in stature to stop at an earlier age is associated with the improvement which has taken place in living conditions. In addition to such an obvious factor in the growth of children as the state of their nutrition, more subtle factors tending to alter the constitution of the population, such as, for example, the reduced mortality of children now as compared with the past, and the smaller size of the average family, may all play some part.

Summary

Observations on the stature of 75 boys and 67 girls, recorded at school over a period of years, have been analysed to determine the distribution of the age at which growth in stature ceases. The data for both sexes constitute censored normal distributions. The distribution for boys was found to have a mean age of 17 years 9·08 months $\pm$ 1·87 months and a standard deviation of 9·96 months, and the corresponding estimates for girls are 16 years 2·71 months $\pm$ 3·44 months and 13·62 months respectively.

I wish to thank the authorities of the two schools for making the records available to me, and the Medical Research Council for providing a grant. My thanks are also due to Dr. G. M. Morant and Mr. M. J. R. Healy for their very helpful criticism and advice.

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TWO CASES OF PRIMARY TUBERCULOSIS AFTER IMMERSION IN SEWAGE-CONTAMINATED WATER

BY

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Primary tuberculous infection is rarely thought to arise by routes other than by aerogenous spread into the lungs or ingestion of infected milk into the alimentary tract. Yet there is ample evidence that other routes of infection are possible, and we are beginning to recognize that extra-pulmonary infection is more common than formerly believed (Miller, 1953). Indeed, it seems that the child may be first infected with the tubercle bacillus from almost any bizarre accident.

Here we report the histories of two children in whom primary tuberculosis followed immersion in sewage-contaminated water. We cannot find any record that this method of infection has previously been reported in England, but we have found reports of five cases in the Scandinavian literature —cases so similar in clinical history to ours that we feel the possibility of this method of infection should be recognized and the sequence of events noted.

The Literature

The five cases are contained in two reports, one of three cases from Oslo (Gaustad, 1947), the other of two cases from Stockholm (Senécal, 1950). All concern children who developed primary tuberculosis within the recognized incubation time after immersion in sewage-contaminated water.

Four of the five children required resuscitation, the other was quickly rescued. All four suffered an immediate febrile illness with vomiting and diarrhoea. At this stage in three children the tuberculin tests were negative and chest radiographs normal. Between two and five weeks after recovery from the enteritis, a more insidious illness developed with malaise and fever unaffected by chemotherapy. Tuberculin tests were now positive and there was radiological evidence of primary pulmonary tuberculosis. The fifth child who had not been ill was examined 10 weeks after the accident and was found to be tuberculin positive; the chest radiograph showed an active primary complex in the right lung. In no instance was there familial tuberculosis or known contact with the disease. Gaustad discovered a sewage effluent from a sanatorium 300 yards upstream from the site of the accident, and previous examination of the water had demonstrated the presence of virulent tubercle bacilli. In Senécal's cases also the children had fallen into sewage-contaminated river water. One negative bacteriological examination was made.

Case Reports

Case 1. In August, 1949, on the second day of a seaside holiday at a resort on the north-east coast of England, a 4-year-old boy ran along the concrete top of a sewer discharging into the sea. At the end he overbalanced, falling into the sea immediately in front of the mouth of the effluent. He went under, was submerged twice, and was being swept out to sea when he was rescued. After revival he was seen by a doctor but was not admitted to hospital, and was apparently well for the rest of the 10-day holiday, but on reaching home began to have sickness and diarrhoea. After a week or 10 days he went to school but was only there three days before he went to bed with a febrile illness, malaise and vague aches and pains. In this condition he was seen by one of us (F.J.W.M.) at the request of his family doctor on September 19, when he had been ill for a week and four weeks after his accident.

On examination he was febrile but not seriously ill, and the only abnormal physical sign was a spleen enlarged about 1 inch below the costal margin. The leucocyte and differential counts did not show anything abnormal; agglutination tests for enteric and abortus fevers were negative. But the tuberculin jelly test was positive and radiographs revealed appearances in the right lower lobe consistent with a primary tuberculous complex. The fever ran the usual course of primary 'fever of onset', settling in three weeks, and the boy was thereafter well until the last week in June, 1950. Then for a week he was vaguely unwell and on July 1, 1950, was seen by his family doctor. On July 4 he was admitted to hospital and seen again by us (F.J.W.M.). This illness was tuberculous meningitis, but after a full course of treatment he made a good recovery, and now three years later is in good health, attending school regularly.

During his first illness his family, in comfortable social circumstances, was examined and no trace of tuberculosis was found: no other contact was known and none has appeared since.

Radiographs taken in October, 1953, have not shown any residual calcification in chest, abdomen, neck or skull, but this does not, of course, invalidate the fact that a shadow consistent with primary infection was visible on the first film in September, 1949.

Case 2. This child, aged 2½, was quite healthy and was staying with his parents at a holiday camp when he fell into an unguarded sewage tank. His father rescued him and after applying artificial respiration took him to the local cottage hospital where he was admitted. There he soon developed severe enteritis which was treated with chemotherapy and subsided. Radiographs of the chest showed right basal shadowing thought to be due to the inhalation of foreign material, but he did not have any symptoms of pulmonary illness, and after 10 days he went home apparently well. Thus he remained for three weeks but then became febrile, and developing a cough, was again admitted to hospital. His illness was at first considered to be caused by unresolved pneumonia, and further radiographs revealed shadows indicating inflammatory changes in the lower and mid-zones in the right lung. As in the previous child, all other laboratory tests, agglutination and stool cultures, failed to give evidence of other infection. Over the next two weeks there was some improvement with chemotherapy and antibiotics (sulphamezathine, penicillin and aureomycin) but thereafter he slowly deteriorated, losing weight and running a high temperature. His tuberculin reaction was found to be positive. Primary tuberculous bronchopneumonia was suspected, and treatment with streptomycin and P.A.S. was begun. Even so improvement was slow. After two months he was still ill, slightly cyanosed, with inspiratory stridor, a brassy cough and signs of consolidation at the base of the right lung. One choroidal tubercle was visible in the fundus of the right eye. Chest radiographs then showed patchy mottling in the left lower lobe with more extensive consolidation on the right side, and enlargement of both hilar shadows. The cerebrospinal fluid was normal. Treatment continued and there was little change for two more months, but thereafter he improved steadily, and one year after his accident was well. A radiograph at this time still showed bilateral basal shadows, and as time has elapsed, calcification has become visible on both sides though more on the right. He has remained well; throughout, his family have been well and there was no known contact with tuberculosis.

Discussion

The account of our two cases reveals an illness strikingly similar to that described by Gaustad (1947) and Senécal (1950). A healthy child inhales and swallows contaminated water during accidental immersion and then has gastro-intestinal symptoms which clear after a few days. Finally after two or three weeks of apparent good health a febrile illness without dramatic clinical signs ensues, and the evidences of disease indicate primary tuberculous infection.

We did not know the previous tuberculin state of either child, but in the north east of England only 2-3% of children are positive at 2 years and 6% by 4 years (Cammock and Miller, 1953). When young children are infected the index case can often be readily found. Neither were we able to investigate the bacteriology of the sewage. We do know, however, that virulent tubercle bacilli have been found in sewage from industrial towns in this part of England (Cummins, Davies and Acland, 1929). From America several authors, including Rhines (1935) and Pramer, Heukelekian and Ragotzkie (1950), have reported the survival of tubercle bacilli for many weeks despite chlorination of sewage. Gaustad and Senécal both warned of the danger from contaminated sewage, and Jensen and Jensen (1942) stressed the danger of bathing near sewage effluents because of the presence of significant numbers of tubercle bacilli.

We think that both our children underwent primary tuberculous infection. The circumstantial evidence is strong enough to suppose that the bacilli were inhaled during immersion, and thereafter a primary complex was formed in the lung. The infection in the second child from standing sewage water seems to have been much heavier than in the first, producing a heavy bilateral primary infection. That the shadow in the first case cleared completely without leaving calcification or other scarring is not exceptional, as this is often observed in children undergoing tuberculin conversion. That the first child developed tuberculous meningitis can be regarded as an unfortunate risk of primary infection, but as 85% of cases of tuberculous meningitis develop within a year of the primary infection the fact is an additional pointer to the nature of the first illness.

We therefore suggest that there is in England as well as in other countries a danger that sewage water may carry tubercle bacilli and that children coming into accidental contact with it may thereby become infected. Closer enquiry might reveal further cases, and we feel the syndrome should be known.

Summary

Two cases of primary tuberculous infection in children of 4 and 2½ years following immersion in sewage-contaminated water are reported. There appears to be a pattern of illness following this accident: immersion sometimes requiring resuscitatation, gastro-enteritis which resolves in a few days,

and thereafter in the third or fourth week a febrile illness which finally reveals itself as primary tuberculosis.

We wish to record our thanks to Dr. J. A. O'Callaghan, the family doctor, for data relating to the first child, and to Dr. Cunningham, of Poole Sanatorium, for permission to use the notes of the second child.

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TWELVE CASES OF LYMPHOBLASTOMATA IN CHILDREN

BY

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The primary purpose of this paper is to illustrate the protean symptomatology of a group of growths known collectively as the malignant lymphomata or lymphoblastomata. Much discussion centres on the exact nomenclature of these conditions, and no attempt is made here to elucidate this matter. Gall and Mallory (1942) discuss the problems involved, and suggest a cytological basis for subdivision; Custer and Bernhard (1948) point out that the cellular structure of lymphatic tumours is extremely labile, and that transition from one apparently distinct type to another is frequently seen, so that an absolute cytological diagnosis by biopsy may be very difficult.

From the descriptive standpoint, with the exception perhaps of Hodgkin's disease, these conditions are relegated to small sections of the average paediatric textbook, emphasis generally being placed on enlargement of lymph nodes in the symptomatology. Arey (1949) does not discuss Hodgkin's disease or lymphosarcoma, stating that they have their counterparts in adult life. Dargeon (1947) states that the physical signs and symptoms of lymphosarcoma will depend on the anatomical site of the affected structures, and says that the nasopharynx, the tonsil and the cervical, or any other group of nodes, may be involved. In a later study (1953), however, he describes more specific cases, and emphasizes the difficulty of diagnosis and management.

Material

The cases are drawn from the practice of the University hospitals of the University of Wisconsin. In all 12 cases the diagnosis was established by biopsy, at necropsy, or by both means. The cytological diagnosis was variously stated to be lymphoblastoma, lymphosarcoma or reticulum-cell sarcoma, each thus being included in the lymphomata as described by Gall and Mallory, or represented in the lymphoblastomata of Custer and Bernhard.

Case Histories

Case 1. This 4-year-old white boy was admitted with a mass on the left cheek which had begun as a small spot 10 weeks earlier and had rapidly increased in size. Sweating at night was an early feature, and shortly before admission deafness in the left ear and epistaxes had occurred. Examination showed a hard, painless mass 4 × 5 cm., anterior to the left ear, involving the tragus and almost closing the auditory canal. The post-auricular, left anterior cervical and axillary nodes were also involved. The other systems were devoid of pathology.

A biopsy suggested lymphoblastoma.

X-ray therapy was begun, but the mass did not regress, the left face being ultimately partially paralysed. A course of nitrogen mustard reduced the size of the mass and nodes, and relieved the facial palsy. Review three months after the initial examination showed recurrence of the original mass and glandular involvement. The patient did not return for further review.

Case 2. This 3-year-old white boy had a history of falling and cutting the inside of the right upper lip. Three weeks later on the outer surface of the same lip a reddish lump appeared, and was thought to be a boil coming to a head. It was reduced in size by hot fomentations, but rapidly grew again. It was incised, but only a small amount of bloody fluid was obtained. It was then excised totally, but the mass recurred. The child was soon afterwards sent to the hospital where examination revealed a large mass involving the right upper lip and extending upwards almost to the zygoma. It was hard and painless and distorted the whole right face. The right sub-maxillary gland was also affected.

A biopsy suggested a reticulum-cell sarcoma.

Fever was a prominent symptom, but there was no clinical or radiological evidence of spread to other systems. Treatment by x rays was begun, and rapidly reduced the size of the facial lesion. He was seen six months later, when the tumour of the lip was greatly reduced, though the sub-maxillary glandular enlargement was still present. The patient did not report thereafter.

Case 3. This 9-year-old white boy had developed a swelling of the left lower jaw some two months before admission. Initially it was regarded as a dental infection, and treated by penicillin. This failing, surgical drainage was carried out, without relief of the pain and swelling. Therefore, a 'cyst' was removed from the outside of the jaw. At the time of admission here, a swelling the size of a grape-fruit involved the left lower jaw and face. Purulent granulations covered the site of the previous incision. Nutrition was unimpaired; a moderate anaemia

present. A clinical diagnosis of actinomycosis was made, but radiographs revealed a destructive lesion of the left mandible and suggested a neoplasm. A biopsy specimen was unsuitable for a full diagnosis.

X-ray therapy was begun, and the mandibular lesion completely disappeared. Three months after the first admission, swellings had appeared in the long bones of the legs, and the child rapidly lost weight. Examination revealed a pallid, cachectic boy, with tumour masses palpable in many parts of the body. Most were attached to bone, a few enlarged lymph nodes were present, the liver and spleen were involved, as were both testicles. Radiographs confirmed widespread metastases to almost all the long bones and the pelvis. He was discharged in a terminal state.

A second biopsy showed a reticulum-cell sarcoma.

Case 4. This 15-month-old white girl was admitted with a history of bruising the right lower chest some two months before. The resultant lump had grown slowly and painlessly. Three weeks before admission, small swellings had appeared in the skin behind the left ear and on the right occiput. Thereafter small painless masses varying in size from pinhead to 0·3 cm. in diameter had appeared in the skin. The mother had been told that they were 'mosquito bites'. Examination showed a well nourished child who played actively, and whose only remarkable features were a hard, painless mass over the right lower ribs, and a multitude of small reddish plaques of varying size in the skin of the scalp, trunk, limbs and labia (Fig. 1). The blood count was at this time normal. A biopsy of one of the skin lesions suggested a lymphoblastoma. Her course was rapidly downhill. The skin lesions increased in size and number, and a terminal leukaemic reaction with a severe anaemia became evident. Treatment with cortisone and T.E.M. (triethylene-melamine) was without avail and the child died at home one week after discharge. Further biopsy of a lymph node again suggested lymphoblastoma.

Case 5. This 3-year-old white boy was well until one week before admission, when the parents noted rapid swelling of the abdomen, failure of appetite, and night sweats. Examination showed an irritable, fevered boy with gross ascites, though a doughy sensation was felt through the fluid collection. A clinical diagnosis of tuberculous peritonitis was considered, but tapping the effusion gave a 'tomato-juice' specimen. This was negative for tumour cells. Soon afterwards signs of fluid in the right pleural cavity appeared, and a mass was felt in the right hypochondrium. A laparotomy was carried out, and the child died suddenly shortly after the operation, at which a large mass involving the intestine and mesenteric glands was found.

Necropsy revealed a tumour, identified microscopically as a lymphosarcoma, involving the peribronchial, mediastinal, mesenteric, omental and retroperitoneal nodes. The lungs, pericardium, pancreas, stomach, small intestine and appendix were invaded. The adrenals were infiltrated, and the diaphragm was encased in neoplasm.

Case 6. This 4-year-old boy had been well until two months before admission here. He then lost his appetite and became pale and listless; there was intermittent looseness of the bowels and constipation. A mass was felt in the right lower quadrant, and a laparotomy was carried out in another hospital. This showed enlargement of all the mesenteric lymph nodes, and a biopsy suggested malignancy.

On admission he was pale and emaciated, the abdomen was protuberant, and a mass 10 cm. wide extended from above the umbilicus to the pelvis. It was firm and painless. A few slightly enlarged glands were palpable in the groins and axillae. The child had a 'coffee-ground' vomit, apparently inhaled some of this, and died after a grand-mal convulsion.

FIG. 1.—The skin lesions in Case 4.

At necropsy it was seen that the small intestine was encased in firm, white, nodular tumour as were the sigmoid, rectum and bladder. The neck of the gall-bladder was similarly involved, and the omenta (gastro-hepatic and colic), and splenic capsule were heavily infiltrated. Several tumour nodules were seen on the liver. The surfaces of the kidneys were studded with whitish masses of irregular shape and size, which involved the cortex but not the medulla. Numerous lesions were present in the anterior part of the costo-phrenic sulcus. The cytological diagnosis was lymphosarcoma.

Case 7. Two weeks before admission this boy, 8 years old and a microcephalic idiot, became ill with fever, listlessness, pallor and some looseness of the stools. A few days after the onset, the left cervical nodes enlarged, and the liver and spleen became palpable and enlarged rapidly. Examination at admission showed a pale, orthopnoeic boy with a distended abdomen due to a grossly enlarged liver and spleen. Both organs were very hard but not tender. A firm glandular mass was present in the right neck, and there was lesser involvement of the axillary and inguinal groups. The child was febrile, and there were signs of a left pleural effusion and of bronchial compression. A radiograph confirmed the mediastinal involvement. The blood at this time showed anaemia with a normal white and differential count. The condition rapidly deteriorated in spite of x-ray therapy. The glandular masses increased, and the blood picture 10 days after admission suggested leukaemia, though a previous gland biopsy showed lymphoblastoma. Death occurred after 14 days in hospital. Permission for necropsy was denied.

Case 8. An 11-year-old white boy had a laparotomy for acute appendicitis, from which he made a good recovery. Two and a half months later he felt weak and listless, and he himself found a lump in his abdomen. There was rapid loss of weight thereafter, and six weeks later he was admitted to this unit. Examination revealed a hard, left-sided, abdominal mass, which moved slightly on respiration, and was painless. The submaxillary, cervical, axillary and inguinal nodes were bilaterally enlarged, as were the epitrochlears. The abdominal swelling had some of the characters of a renal tumour, but pyelography and barium enema showed that it was extra-renal and extra-colic. Biopsy of a mesenteric gland showed lymphosarcoma. The boy died soon afterwards.

Case 9. The complaint in this case was of the appearance of a hard, painless, abdominal swelling in an otherwise healthy 18-month-old girl. The process had lasted for three weeks before admission. Fever, anorexia, listlessness and insomnia had been noted, but all urinary and gastro-intestinal symptoms were absent. Examination showed a coconut-sized mass stretching from the left upper quadrant to the left iliac fossa. The liver was also felt and was thought to contain nodular masses.

Radiotherapy was begun, causing rapid diminution of the abdominal tumour, and laparotomy was carried out. This revealed a retroperitoneal mass not involving the adrenals or kidneys. She was readmitted four months later, and the previously noted mass was felt only with difficulty, and the liver was thought to be smaller. A 'brassy cough' suggested mediastinal involvement, and radiographs confirmed this. Soon afterwards the abdominal tumour increased, gross anaemia occurred, and the child died.

Necropsy revealed a retroperitoneal mass displacing the stomach, spleen and pancreas. The liver was heavily infiltrated with tumour metastases, as were the anterior and superior mediastina. The pre-aortic lymphatics were also heavily involved. Microscopy confirmed the diagnosis of lymphosarcoma.

Case 10. This white girl, age 8 years, had bruised her left groin. Fever followed, and a lymphatic swelling was discovered. A biopsy was done, and revealed a 'small-cell lymphoblastoma'. She was seen in this unit three months after the onset of symptoms, and after radiotherapy had been begun. The residua of the enlarged nodes were palpable, but there was no evidence of further involvement. Six months later the nodes of the left anterior triangle and supraclavicular areas were enlarged and the spleen was felt. There was local recurrence in the left inguinal region. Four months later, that is one year after the onset, she was rapidly deteriorating in spite of further x-ray therapy. Thereafter she was lost sight of, but her local physician was of the opinion that she was in the 'terminal' stages of the illness one month after final discharge.

Case 11. This 9-year-old white girl became ill 3 months before admission here. The initial symptoms were of fever and swelling of the glands in the left neck. These were reddened, somewhat tender, and adherent to the deeper structures. A diagnosis of tuberculous lymphadenitis being made, the child was admitted to a sanatorium. There a negative tuberculin test led to the removal of a node, and microscopy suggested a reticulum-cell sarcoma. Examination revealed a pallid, listless child. The left cervical nodes were enlarged and slightly tender. The corresponding nodes on the right were also involved as were those of the right axilla. The spleen was felt 6 cm. below the costal margin, being firm and not tender. There was a hypochromic anaemia, with a normal white and differential count. Enquiry failed to elucidate her further course.

Case 12. This girl, 2 years old, was seen in the eye department with a 2 × 3 mm. mass in the inner canthus of the right eye which had been present for one month. It did not seem inflammatory, and obscured the caruncle without interfering with lacrimal drainage. The mass was removed, and section showed it to be a lymphoblastoma. Follow-up over a period of two years, with extensive clinical and x-ray surveys, has failed to show evidence of local recurrence or metastatic spread.

Clinical Features

The clinical features are summarized in Table 1, and the relevant haematological detail is given in Table 2. A great variation in the clinical picture, quite unrelated to a fairly constant cytological pattern, is seen. Thus the initial symptom in three cases (Cases 6, 8, 9) was of a painless intra-abdominal mass, and in two (Cases 10 and 11), enlargement of lymph nodes. Three cases (Cases 1, 2 and 3) each presented with a mass on the face. In Case 5 there was a rapid onset of ascitic swelling of the abdomen, clinically simulating an acute tuberculous peritonitis, the true diagnosis only being considered when a blood-stained effusion was found. Similarly in Case 11, the onset of fever and painful swelling of the neck nodes led to an erroneous

TABLE 1
SYMPTOMATOLOGY

Case	Initial Symptom	Fever	Pallor	Anorexia and Listlessness	Lymph Node Involvement (Clinical)	Duration before Admission to Hospital	Total Duration
1	Swelling of face	no	no	no	yes	10 weeks	Followed for 4 months
2	Mass on right upper lip	yes	no	no	yes	1 month	Followed for 6 months
3	Swelling of left jaw	yes	yes (in later stages)	In later stages	yes	2 months	Terminal after 3 months
4	Mass on right lower chest with skin lesions	yes (later stage)	not initially	no	yes	2 months	Died after 4 months
5	Swelling of abdomen (acute)	yes	no	Anorexia only	no	1 week	Died after 1 week
6	Swelling in abdomen, gastro-intestinal upset	no	yes	In later stage	no	2 months	Died (inhalation) after 2 months
7	Fever: gastro-intestinal upset, gland swelling	yes	yes	yes	yes	2 weeks	Died after 1 month
8	Localized mass in abdomen	no	yes	yes	yes	4 months	Lost sight of
9	Mass in abdomen	yes	no	yes	no	3 weeks	Died after 5 months
10	Swelling of groin glands	yes	no	Later stage	yes	3 months	Terminal after 8 months
11	Swelling of neck glands	yes	yes	yes	yes	3 months	Lost sight of
12	Small growth inner canthus right eye	no	no	no	no	1 month	Alive after 2 years

diagnosis of tuberculous lymphadenitis. The patient was confined to a sanatorium for two months before biopsy clarified the condition. The history and early clinical course in Case 3 were most misleading, and actinomycosis was the clinical diagnosis; radiographs, however, showed widespread mandibular destruction suggestive of neoplasia. Pallor, anorexia and listlessness were common features. In Cases 7, 10 and 11, a prominent, or in Case 7, the only, initial complaint was fever. Trauma was an associated factor in Cases 2, 4 and 10, and in two instances seemed definitely to have preceded the appearance of the primary lesion. Case 4 was referred initially as a dermatological problem, the lesions having previously been dismissed as mosquito bites. The course in Case 7, with massive glandular enlargement and hepatosplenomegaly, was perhaps more suggestive. Case 12 was diagnosed only by biopsy.

The paucity of symptoms in relation to widespread anatomical lesions is very striking in Cases 5, 6 and 9. The first two reflect the condition reported by Guthrie (1948) in describing a case with similar necropsy findings.

The table of haematological findings shows that a severe hypochromic anaemia was the usual state. In this connexion Sugarbaker and Craver (1940) in reviewing a series of adult cases, state that the blood picture is non-specific in lymphosarcoma, 70% of their patients having a haemoglobin level of 80% or more.

Two cases (4 and 7) showed a leukaemic picture

TABLE 2
BLOOD FINDINGS

Case	Hb (g. %)	R.B.C. (millions)	W.B.C. (thousands)	Differential White Count
1	12·3	3·93	4·85	Normal
2	8·4	3·0	6·9	Normal
3	Initial 10·0	3·5	8·1	Normal
	Terminal 5·1	1·9	6·05	Normal
4	Initial 11·3	3·92	8·0	Normal
	Terminal 8·5	3·48	151·0	Abnormal—leukaemic picture
5	12·5	4·5	10·6	Polymorph response
6	9·0	3·8	6·5	Normal
7	Initial 12·0	4·85	7·3	Normal
	Terminal 8·4	2·5	18·65	Abnormal lymphocyte response—leukaemia
8	8·4	3·64	8·7	Normal
9	8·0	3·9	18·0	Normal
10	11·4	4·2	2·8	Normal (x-ray therapy)
11	10·0	4·4	8·5	Normal
12	13·5	5·1	8·3	Normal

Hb = Haemoglobin.
R.B.C. = Red blood count.
W.B.C. = White blood count.

after a relatively short time. The bone-marrow biopsy in the latter was not, however, typical of acute leukaemia. This phenomenon of transformation does not necessarily negate a diagnosis of lymphoblastoma, having been previously observed by Custer and Bernhard (1948) and by Warthin (1931). The latter noted leukaemic transition in nine of 134 cases of lymphosarcoma, and observes that mycosis fungoides, of which Case 4 might be a variety, could become leukaemic terminally. Fraser (1925), however, demonstrated mycosis fungoides as a type of lymphosarcoma.

Table 1 shows that the course was fulminant in many cases, though full information on this point is lacking in view of the incomplete follow-up. However, of those where definite information was available, the majority were dead, in spite of treatment, in six months, and in five cases the disease was fatal in four months or less.

Treatment

Radiotherapy was tried in all cases, except in Case 12, where only simple excision was used. In addition, Case 7, and Cases 1 and 10 received T.E.M. (tri-ethylene-melamine) and nitrogen mustard therapy respectively. The response was disappointing, though temporary benefit was occasionally seen.

Summary

Twelve cases of lymphoblastoma in children are presented; none was thought to be of the Hodgkin variety. The symptoms and physical signs are seen to be protean, and in some cases bear no relation to widespread anatomical lesions. The process in the majority is rapidly fatal. The difficulties of diagnosis are discussed, the initial picture being misleading, here varying from actinomycosis of the jaw, tuberculous peritonitis, and benign lesion of the caruncle, to scrofula.

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SCROTAL GANGRENE IN A NEWBORN BABY

BY

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Not more than 51 cases of gangrene occurring in the newborn have been reported so far, and only some 240 instances of idiopathic gangrene of the scrotum at any age are on record. A case of scrotal gangrene in a newborn baby is reported here because this condition must be extremely rare and because it illustrates the interesting fact that the newborn are liable to infection by common organisms of usually low pathogenicity with results similar to those caused in the adult by more virulent micro-organisms.

Case Report

A primigravida, aged 21, was admitted to the Maternity Department on June 16, 1949. She was 36 weeks pregnant and the foetus presented by the vertex (L.O.A.). There were signs of pre-eclamptic toxaemia (blood-pressure 180/110 mm. Hg, oedema of the feet, ankles and abdominal wall, but no albuminuria). Her blood group was A Rh negative. The Wassermann reaction was negative. She was treated with rest in bed, sedatives and restriction of salt. Her condition improved and, on July 8, she was normally delivered of an apparently healthy male infant, weighing 7 lb. 12 oz., after a labour lasting 23 hours. The infant cried immediately after birth, and no injections into his body or into the umbilical cord were given. He was fed with Half-Cream National Dried Milk from the beginning as the mother (who was unmarried) wished to resume work as soon as possible and refused to breast feed.

On July 17, the infant, now 9 days old, was noticed to be irritable; his temperature was 100·2° F. and the scrotum was slightly swollen. Penicillin, 50,000 units, was injected intramuscularly, four-hourly for 10 days. On July 17 the temperature rose to 102·4° F. but the infant's general condition was remarkably good. The scrotum was grossly swollen and tense, its lower half was reddened; the swelling was fluctuant and transilluminable, and extended up to the left external inguinal ring. Aspiration, inserting a small-bore needle well above the reddened area, produced 4 ml. of clear, straw-coloured fluid from the hydrocoele. On July 19 the infant's general condition was still good, but the temperature rose to 100·2° F. The lower half of the scrotum was discoloured and appeared to be about to slough. A swab was taken from this area. On July 20 the temperature was 102·2° F. again, and the diagnosis of scrotal gangrene was unmistakable (Fig. 1).

The pathologist reported that the swab showed necrotic pus cells, Gram-negative bacilli and Gram-positive cocci, and culture gave a good growth of coliform bacilli and scanty, non-haemolytic staphylococci.

Treatment with ¼ g. of sulphatriad, four-hourly, was begun and continued for seven days. Sulphathiazole powder with 1% proflavin hemisulphate was applied locally.

On July 31 the slough was separating. The infant's weight was 9 lb. On August 8 the slough had almost completely separated and there remained a scrotal ulcer, ½ in. in diameter, covered with black, necrotic tissue centrally and with pus peripherally. On August 17, the only abnormality was a small dimple at the most dependent part of the scrotum which was everywhere covered by normal skin, but appeared to be somewhat small due to the loss of tissue. One testicle was palpable in the

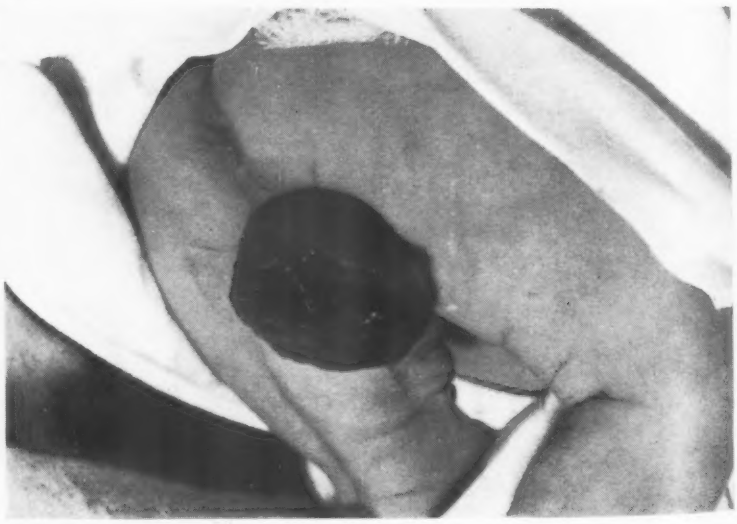

FIG. 1.

scrotum. The infant, now 45 days old and weighing 10 lb. 12 oz., was discharged from hospital.

In October, 1953, the child was re-examined. He was a healthy boy, now over 4 years old, who had, according to his grandmother, never given any trouble. The scrotum appeared perfectly normal; the left testicle was descended, the right could be felt in the inguinal canal.

Discussion

Rarity of the Condition. Gangrene in the newborn is a rare condition but the number of cases reported by obstetricians and paediatricians is increasing (Brown and Smith, 1951; Delerue and Courtin, 1952; Stokes and Shumacker, 1952). Such gangrene affects, in order of frequency, the lower extremities, the upper extremities, the viscera, the gluteal region. Scrotal gangrene of the newborn would appear not to have been recorded before; Carver (1939) quotes Campbell (1922) as describing such a case in an infant 5 days old, but no such case is in fact mentioned by Campbell.

Aetiology of Idiopathic Scrotal Gangrene. Clinically the present case conformed closely to the usual descriptions of idiopathic scrotal gangrene. Barclay and Hendrick (1948) mention as characteristic features of this condition (1) sudden onset in an otherwise healthy male; (2) rapid progression of the gangrene; (3) total absence of the usual causes of gangrene; (4) extensive and relatively constant areas of gangrene, the testes, spermatic cords and inguinal regions being rarely affected; (5) a tendency for spontaneous repair.

The term idiopathic, 'a mere cloak for ignorance' (Robinson, 1946), implies that the aetiology of the condition is obscure. Two theories predominate in the modern literature. According to Mansfield (1946) in this country, and to Barclay and Hendrick (1948) in the U.S.A., idiopathic scrotal gangrene is a vascular disaster of infective origin, analogous to cavernous sinus thrombosis. The infection is not believed to have any specificity other than the existence of a pathogenic organism which causes rapid thrombosis in the vessels of the scrotal septum with consequent necrosis of the area supplied by these vessels. The fairly constant pattern of the sloughing area is thus explained on a vascular basis. This theory stresses the importance of vascular changes in this particular type of infection rather than questions the basically infective character of the condition.

Campbell (1922), Mair (1945), Robinson (1946) and others suggest that idiopathic gangrene of the scrotum is but one form of fulminating erysipelas. Mair collected 44 cases in which the bacteriology of scrotal gangrene has been investigated. In 28 of these, haemolytic streptococci were found either in pure culture or with staphylococci; only once were coliform bacilli isolated.

In the present case *Bact. coli* (and non-haemolytic staphylococci) were isolated from the lesion. While admitting that treatment with penicillin, which was begun two days before the swab was taken, may have eliminated haemolytic streptococci, the failure of penicillin to bring down the temperature, and the prompt response to sulphonamides, strongly suggest that the responsible organism in this case was a coliform bacillus. This may be taken as an illustration of the experience that a microorganism of usually low pathogenicity may cause in the newborn infant a serious condition which in the adult is usually produced by a different, more virulent organism. Comparable occurrences are meningitis caused by coliform bacilli and pneumonia by coliform bacilli, non-haemolytic streptococci, *Staphylococcus aureus* or *Staphylococcus albus*, in the newborn.

Aetiology of Gangrene in the Newborn. Gangrene in the newborn may be due to mechanical causes such as pressure on a particular part *in utero*, pressure necrosis of a prolapsed part during labour, or trauma at delivery, though the liability to gangrene of the newborn tissues is very low, as every obstetrician knows; the sometimes monstrous appearance of the face in face-presentation, or of the external genital organs in breech-presentation at the conclusion of a prolonged labour in such cases regresses to normal in a matter of hours. No such mechanical cause could have been operative in the case under discussion, as the foetus presented by the vertex, and gangrene set in several days after birth.

Mills (1949) and others after him have described arterial lesions resulting in cutaneous ulceration of the gluteal region and the lower limbs. This 'new neonatal syndrome' is strongly suspected to be due to accidental injection of nikethamide into an artery of the umbilical cord. In two of Mills' cases there was discoloration, but no ulceration, of the scrotal skin as well. This mechanism can be excluded in the present case, as no such injection was given and as the morbid process set in as late as nine days after birth.

Gangrene may be a complication of umbilical sepsis (Sheldon, 1936). Delerue and Courtin (1952) hold that infective arteriolitis may be responsible for multiple areas of gangrene associated with bronchopneumonia and other infections; the prognosis in such cases is almost always bad. There was no evidence of a generalized infection in the present case.

A search of the literature has failed to bring to light a single case of scrotal gangrene as a spontaneous complication of hydrocoele. Only one case (Finch), dating back to 1887, was found in which scrotal erysipelas and gangrene was described as the result of infection produced by aspirating a hydrocoele. In the present case the needle was inserted well above the reddened area in which gangrene later occurred.

Arterial spasm, with or without thrombosis or embolism, have been held responsible for gangrene of the newborn by Gross (1945), Lewis (quoted by Aird, 1949), and Stokes and Shumacker (1952). The fact that the overwhelming majority of all cases described occurred within 15 days after birth suggests some relationship to post-natal circulatory changes. (It has been suggested that intra-vascular injection of nikethamide may be followed by discharge of pituitary hormones and of adrenaline, producing vaso-constriction and ulceration in the new neonatal syndrome described by Mills.)

Conclusion

In our present state of knowledge (or rather ignorance) it is assumed that scrotal gangrene in the case presented was due to local infection with coliform bacilli which produced profound vascular changes.

Summary

A case of scrotal gangrene occurring during the neonatal period is described. The interest of this extremely rare occurrence lies in the fact that a condition usually caused in adults by haemolytic streptococci was produced in this newborn infant by coliform bacilli.

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NEONATAL THROMBOCYTOPENIC PURPURA IN TWO INFANTS

BY

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Cases of purpura in the newborn have been recorded fairly frequently, and Robson and Walker (1951) have recently reviewed the literature of some 52 cases. Three types of congenital purpura are recognized: (1) Purpura when the mother is affected; (2) purpura when the mother is normal; (3) purpura associated with hypoplasia of the bone marrow.

The essential characteristics in the diagnosis of idiopathic thrombocytopenic purpura in the adult are: (1) A platelet count of 100,000 or less; (2) no other cause for purpura; (3) normal clotting time; (4) prolonged bleeding time; (5) bone marrow normal or showing increased megakarocytes. The same criteria may be applied to neonatal cases. The literature shows over 30 such cases of congenital thrombocytopenic purpura occurring in the newborn in which the mother had the same disease, and amongst these McAlenney and Kristan (1949) found nine instances in which splenectomy had been performed on the mother.

In the following account the mother had idiopathic thrombocytopenic purpura in 1938 when she was 15 years old, and both her infants, born in 1950 and in 1952, showed neonatal purpura.

Case Report

I.M. was born in 1922. She first attended Selly Oak Hospital in 1938 when she was admitted with severe menorrhagia; her condition was diagnosed as thrombocytopenic purpura, and after transfusion the spleen was removed.

She next attended the Out-Patient Department in 1948 when she contemplated marriage, and wished to know if pregnancy was contraindicated. In the intervening 10 years her health had been good, but she continued to bruise easily and her periods, which lasted four days, were rather heavy.

On examination she showed a few ecchymoses on arms, legs and chest. The capillary resistance test of Hess was positive.

The bleeding time was 10 minutes and the clotting time 3½ minutes. A blood count gave Hb 11·7 g. %; R.B.C.s, 4,000,000; leucocytes, 6,400; platelets, 47,000; and reticulocytes less than 1%. The blood was Rh positive, the erythrocyte sedimentation rate was 3 mm. in one hour and clot retraction was normal.

She was advised to attend hospital for antenatal care and delivery should she become pregnant.

On March 14, 1950, she reported at the ante-natal clinic. She was 12 weeks pregnant. Her general health was good, and a blood count showed: Hb, 13 g. %; R.B.C.s, 4,700,000; platelets, 56,000; clotting time, 3½ minutes and bleeding time, 2½ minutes.

She attended regularly and remained well. On September 20 she was admitted in labour, which proceeded normally until after the birth of the placenta, when she rapidly lost 30 ounces of blood; one and a half hours later she again had a brisk loss of 12 ounces.

On September 22 a blood count gave Hb, 9·1 g. %; R.B.C.s, 3,030,000; M.C.H., 30; leucocytes, 16,700; platelets, 27,200; clotting time, 3 minutes; bleeding time 4½ minutes; prothrombin time, 21 seconds; and prothrombin consumption poor.

FURTHER BLOOD COUNTS OF D.M.

Date	Hb (g.%)	R.B.C.s	Platelets
16.10.50	8·8	2,670,000	Less than 10,000. Group AB.Rh.+
19.10.50	8·7	2,670,000	66,000
2.11.50	8·0	2,560,000	56,000
8.11.50	7·4	2,300,000	46,000. Blood transfusion
11.11.50	13·0	4,300,000	
23.11.50	10·6	3,930,000	78,000
21.12.50	11·4	3,900,000	94,000
15. 2.51	11·6	4,370,000	131,000
12. 4.51	12·3	4,090,000	244,500
5. 7.51	11·9	3,410,000	341,000
25. 7.51	11·0	3,400,000	340,000
4. 9.52	11·4	3,340,000	220,400

The puerperium was normal. There was no further bleeding.

D.M., a boy, was born on September 20 (birth weight 8 lb. 13 oz.). A petechial rash was noticed at birth.

Bruising on both scapulae and on the arms was noted on September 27. A petechial rash was seen on the scalp, buttocks, back and limbs; the heels were bruised. The general condition was good, and the spleen was not felt.

A blood count on September 22 gave: Hb, 14·8 g. %; R.B.C.s, 4,200,000; M.C.H., 35 mm.; platelets, 50,500;

clotting time, 3 minutes and bleeding time, 6 minutes. On that day the scrotum and heels were discoloured, but the petechial rash had almost disappeared. Three days later the petechiae and bruising were fading, there was no haemorrhage. Meconium was normal. On September 27 haemoglobin was 12·8 g. % and platelets 10,000.

After the initial post-natal phase the child's progress has been very good. No further petechiae or abnormal bruising have occurred, and he remains quite normal.

In January, 1952, I.M. again attended the ante-natal department. Her health was good, but a few petechial spots were seen on the legs.

BLOOD COUNTS DURING SECOND PREGNANCY

Date	Hb (g.%)	R.B.C.s	Platelets
20.3.52	12·7	4,670,000	140,000
17.4.52	13·0		74,000
26.4.52	15·2	5,000,000	121,000
29.5.52			314,000
12.6.52		4,010,000	368,920

On June 25, 1952, she was delivered normally of a full term girl (J.M.) weighing 7 lb. 13 oz.

There was no abnormal bleeding.

On June 24 10 mg. of Vitamin K was given, and on June 25 a further 10 mg. A blood count on June 26 gave Hb, 15·2 g. %; R.B.C.s, 5,080,000; M.C.H., 29·9; platelets, 121,920; clotting time, 3 minutes 45 seconds and bleeding time 2 minutes.

The puerperium was uneventful, and the patient and her baby went home on the tenth day. Since then I.M. has been seen frequently, and has had normal blood counts and a platelet count above 100,000.

No bruising or petechiae were seen at birth of J.M. at 5.30 a.m. but during the day petechial haemorrhage appeared on the scalp, buttocks and beneath the binder. On the next day the infant was very well, but the petechial haemorrhages persisted. She had no melaena, and passed normal meconium.

BLOOD COUNTS OF J.M.

Date	Hb (g.%)	R.B.C.s	Platelets
25.6.52			
Cord blood	14·6	3,870,000	
Heel blood	19·6	5,400,000	24,400
27.6.52	19·6	5,820,000	34,920
29.6.52	18·7	5,480,000	65,760
30.6.52	19·8	5,800,000	29,400
2.7.52	18·8	5,490,000	27,450
7.8.52	13·3	3,680,000	22,000
4.9.52	10·6	3,330,000	199,800
3.10.52	10·6	3,560,000	270,000

The infant's progress was satisfactory with a steady gain in weight, and no recurrence of bruising or petechiae.

Comment

The mother, who was known to have had thrombocytopenic purpura at the age of 15 when her spleen was removed, still showed evidence of this disease 10 years later. She did not bleed severely and her general health was good. During the first pregnancy she had petechial rashes and there was a small post-partum haemorrhage after a normal delivery. The platelet count was low during pregnancy and after delivery. The male infant showed more bruising and rash than his sister. Although there was no intestinal or other haemorrhage, his haemoglobin dropped to 7·4 g. %, and his platelets remained below 72,000 until after the blood transfusion on November 8 at the age of 6 weeks. The progress since then has been entirely satisfactory with normal blood counts since the age of 3 months.

The female infant was less affected than her brother, and their mother was in very good health during this second pregnancy. Her haemoglobin, R.B.C.s and platelets were normal, and after delivery the platelets were 121,920. Her daughter's blood counts remained satisfactory in spite of the low platelet count which rose to over 100,000 after 10 weeks of age. Since then she has been well, and her blood counts have all been normal.

The hereditary factor in this disease has been discussed by a number of writers:

Sanford, Leslie and Crane (1936) describes a case where the infant was born with purpura. The mother suffered from petechial haemorrhage, and had a low platelet count; her mother also had purpura. Morrison and Samwick (1945) record a similar case of grandmother, mother and infant.

In our family no further history of purpura could be elicited. There is no evidence of thrombocytopenic purpura in her mother.

Both children appear to be free from the disease at present, and it is impossible to say whether they have inherited the factor causing the disease, or whether this tendency passed through the placenta before delivery, giving rise to a temporary thrombocytopenia. The rapid subsidence of the purpura and thrombocytopenia after the establishment of independent life favours the second assumption, and only prolonged observation will show whether the disease remains latent in the two children.

Summary

Thrombocytopenic purpura occurring in two infants whose mother was known to have had the disease at the age of 15, when splenectomy was done, is described.

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